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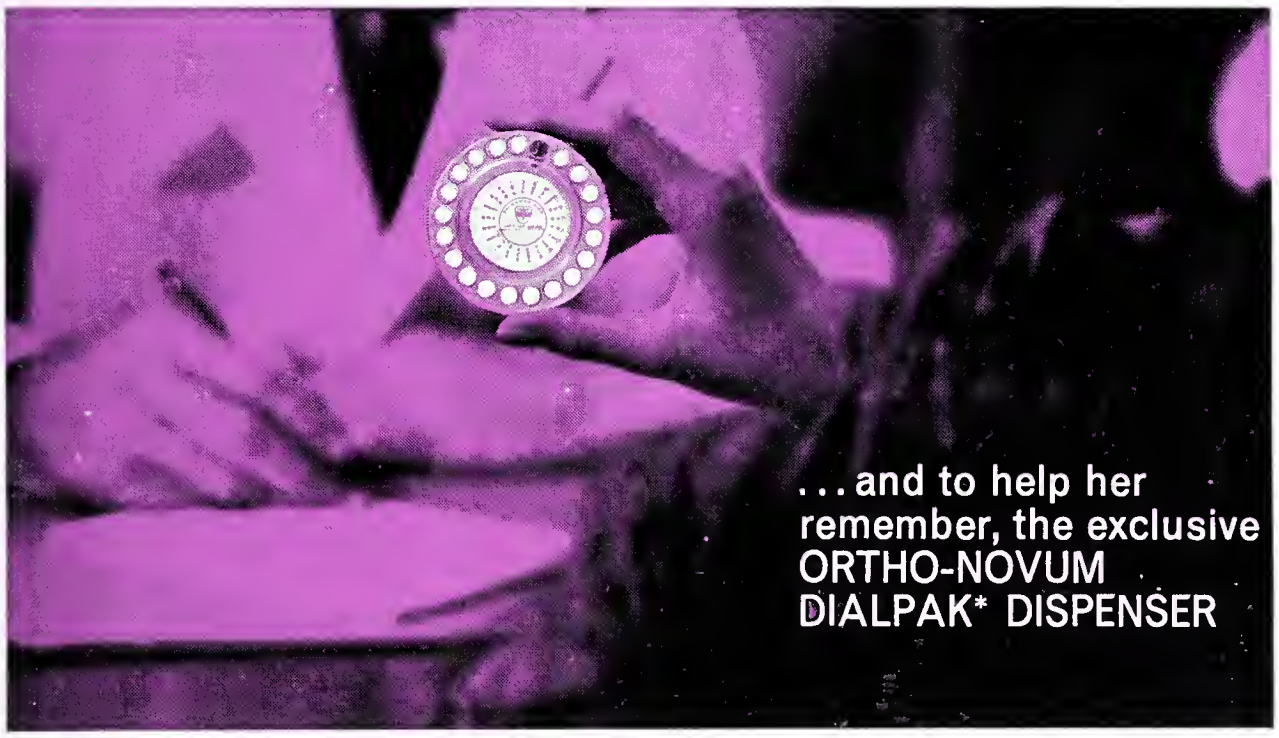

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Editorial

A fundamental dictum underlying the treatment of any patient is profound respect for the integrity of the individual. Such an affirmation bears constant repetition when one considers the management of a patient who suffers from neoplastic disease. It is the opinion of this under trained, ill-experienced medical student that the cancer patient all-too-often is felt to be an exception to the above precepts. It is a situation almost unique to this group of patients that the diagnosis, though known, is not admitted, and the prognosis is hidden in a mire of eventualities. Often this stems from the physicians tendency to attribute to the patient the same amount of courage he accredits to himself. Often this is not the case. The cancer patient is a member of a very select group of human beings. He seems to be able to muster courage somewhere in the depths of his own being that fosters in him a will to live, while realistically facing the frightening prognosis which is his. It is an attribute of the very highest human order. The great paucity of psychogenic or functional complaints bear witness to this impression. With this introduction to the cancer patient we would now discuss a concept of palliative radiotherapy in the management of these cases.

Palliative therapy is very difficult to define. In a sense, it is the treatment of a symptom as opposed to a disease. Yet, it is done out of an understanding rather than ignorance. The treatment is to alleviate one symptom of a disease, and that symptom is most commonly pain. No pretense is made to curing, controlling or preventing further dissemination of the disease. The old French proverb: "There is no such thing as a disease, only sick people" is most relevant to this discussion. Palliative therapy involves consideration of the whole patient. It includes a decision as to the therapy that will best alleviate the symptomatology with least discomfort, and the investigations which will be of most value, but at the same time, least traumatic. In the management of childhood malignancy the parents also must be considered. In effect, you must treat three patients.

Palliation is abused most commonly in one of two ways. It is neglected or abused. The former often stems out of ignorance of the palliative procedures available eg. radiotherapy, chemotherapy etc. It must always be recalled that the cancer patient has a definite and inherent right to treatment just as does any other group of patients in medical practice. The abuse of palliation is more malicious. For here the sum total of investigation and treatment causes greater disability than did the symptoms. It is the pitfall of the over zealous physician, or surgeon, who can't see the patient for the disease. Good palliation lies in a path midway between these two extremes. It considers not only the nature of the neoplastic disease process, but also the psychologic, socio-economic and yes, religious backgrounds of the patient. Good palliative procedures are evidence of sound medical practice for which the cancer patient will be ever grateful. The principles on which sound palliative measures are based require much research and even more soul searching. However, effective palliative therapy is in the highest tradition of the medical profession.

R.P.O.

The Systemic Effects of Malignancy

M. E. Petersiel, 6T5

Malignant disease may manifest itself in a myriad of ways. While the elinical findings are ordinarily those of a elassieal, well defined disease pattern, aeeumulated experienee and eomprehensive investigation have revealed a multitude of sceondary effeets. In this review, sueh effects due to loeal invasion, erosion, pressure and obstruetion will not be discussed. These will obviously depend on the position and aetivity of the tumor. What will be dealt with is the faseinating field of systemic, seeondary effeets for which no positional or loeal reason ean be found.

These phenomena were noted by Campbell De Morgan, diseussing *Cancer* before the Pathological Society of London in 1874. He stated at that time that "a loeal eaneer in an ordinary situation may give rise to a general disease of a structure totally different from it"—and the eonsidered remarks of a prominent pathologist proved prophetie, surely beyond his expeetations. Little is noted of these symptoms until the late Hurst Brown, in 1927, diseussed the appearanee of a "bearded woman with diabetes", obese in her trunk but not in her extremities. Pathological examination revealed, five years before Cushing's syndrome was enunciated, no adrenal abnormality, but instead an anaplastic, oat cell earcinoma of the bronehus.

Sinee that time, a multiplicity of events whieh may be attributed to malignancy have been found throughout the body. In many eases the syndromes mirror those of non-malignant disease, often occurring with suddenness, and following a florid eourse. Dramatic recession may oeeur when the malignaney is treated by radiation, ehemotherapy, or removal. Yet the pieture is not elear cut, for the expeeted regression of symptoms often may not result after treatment. Patients who exhibit these abnormalities, espeeially of sudden onset in unusual age groups, must thus be earefully and fully examined for malignant disease.

A. Dermatologic

1. *Nonspecific*

Many nonspecific changes are noted. Pruritus is eommon in Hodgkin's diseasc. Multiform, eczematoid rashes are seen as well. It is postulated that these disorders are due to a skin response to nonspeeifie toxins, formed by the tumor or released by its local action. Iethyosis, hypertriehosis may be seen in eldery patients. A herpetiform and an exfoliative dermatitis may bc noted. A multitude of erythematous eruptions is also found.

2. *Acanthosis nigricans*

This lesion, oceurring rapidly, in a patient over 40 years of age, is assoeiated with a visceral malignant adenocareinoma. The appearance of a darkly pigmentcd pruritie lesion, soft, eonfluent and verrueal in naturc, occurring in body folds, umbilieus, pcrianal and periumbilieal regions is the elassieal deseription. Of those diagnosed, 90% havc rcsultcd from intraabdominal lesions, the remainder from breast and lung. Almost 80% have appeared before the lesion was diseovered.

3. *Erythema gyratum repens*

Taken to be a toxie response by the skin, this lesion eonsists of a gyrate, erythematous, macular eruption giving the skin a knotty pine appearanee. Allergens are presumed to arise from the products of tumor neerosis. It is found with adenoeareinoma of the breast and anaplastic oat cell tumor of the lung.

4. *Others*

These inelude hyperkeratoses assoeiatcd with neoplasms of skin and the abnormal pigmentation of pituitary adenoma origin.

B. Connective Tissue Disorders

1. *Dermatomyositis*

Dermatomyositis is perhaps the best known of the "collagen diseases" assoeiated with malignaney. Varying rcports indicate 10-30% of those with the condition have a malignant disease as well. The correlation is most obvious when the patient again is over 40. There is no apparent relation between skin reaction and tumor spread. The elinical picture is the eustomary violaeeous, erythcmatous rash ovcr the faee and neek, the heliotrope eyelids due to subeutaneous telanagiectasis, the red, atrophic knuckles associated with proximal muscle weakness and astrophy. Neural involvement, shown by decreased tendon reflexes is present at times. The clinieal course of the disease is aeeelerated by underlying malignaney. Commonly related lesions are those of stomach, lung, breast, ovary (often bilateral), lymphoma and sareoma. Thc pathogenesis is eonfused, perhaps concerned with abnormal immune meehanisms related to the action of eatabolie products of the neoplasm. Thesc paticnts reveal eutaneous immediatc hypersensitivity to extracts of their own tumor. Hormonal factors may also be involved but the issue is far from elarified.

2. *Scleroderma*

Scleroderma is associated both with carcinoid tumor, and with terminal alveolar cell carcinoma of the lung. Other collagen disorders more rarely noted include disseminated lupus erythematosis and some cases of vasculitis.

3. *Arthritides*

Polyarthritis, in a rheumatoid form, is a concomitant of some cancers of prostate and lung. Bone pain, muscular weakness, redness and tenderness of the joints are found. The lesions is often associated with clubbing and is probably related to the skeletal changes of that disorder.

4. *Pulmonary Hypertrophic Osteoarthropathy*

Technically, clubbing of the fingers is a separate entity from this syndrome. A form of rapidly developing painful clubbing is seen with entrathoracic tumors, and is relieved with treatment. The full blown syndrome of osteoarthropathy includes periosteal proliferation and the formation of the new bone at the distal ends of long bones. This is found with bronchogenic carcinoma, and in an even higher percentage of the more rare mesotheliomas. Symptoms include the acute onset of deep seated, burning bone pain, aggravated by dependency and tenderness over bones. Here, the similarity to rheumatoid arthritis is most marked, with symmetric, migratory arthritis, afflicting the larger joints with heat, redness, and limitation of motion. Painful digits in arms and legs are common. This variety of symptoms may precede the pulmonary symptomatology by months, and is usually relieved within a day of therapy.

5. *Pachydermoperiostosis*

This syndrome, apparently a variant of hypertrophic osteoarthropathy, results in acromegaloid features, pronounced clubbing, and a skin eruption—cutis verticis gyrata. It is associated mainly with intrathoracic neoplasms.

C. Hematologic Disorders

Bone marrow metastases are responsible for leukoerythromblastosis—the appearance of normoblasts and early myeloid cells in the peripheral blood. Myelophthisic anemia, leucopenia, and thrombocytopenia may result from marrow infiltration as well. However, several disorders arise without this mechanism.

1. *Anemia*

Anemia is the best known of these abnormalities. It is not associated with blood loss, infective processes or renal impairment, but presents a similar picture of normochromic, normocytic anemia. Iron studies reveal a hypoferremia in some cases, in others a hyperferremia with decreased iron ultization and impaired erythropoiesis. Hemolytic types of anemia are associated with teratomas of the ovary, reticuloendothelial tumors, and other solid neoplasms. A Coombs test is rarely positive in these cases, but varying dysproteinemias have been studied in an attempt to stick an autoimmune label on the disorder. A definite anti-red blood cell antibody has been found only with ovarian teratoma. Again, a hemolysin arising from tumor tissue has been seen only once, with no confirming reports. A final cause of anemia is marrow aplasia, resulting from thymoma and leukemia.

2. *Erythrocythemia*

Erythrocythemia, probably not a true polycythemia has been found in 3% of patients with renal carcinoma. Conversely 2% of patients with polycythemia have been found to have renal carcinoma. This variant presents clinically with no splenomegaly, normal oxygen saturation, white blood cell count and platelets, but with increased red blood cell mass and plasma volume. It has been found, as well, with malignant renal tumors, hydronephrosis and polycystic disease. Other malignancies involved include hepatoma, metastatic carcinoma of the lung, prostate, and cerebellar hemangioblastoma. Pathogenesis is postulated to be an increased secretion of erythropoietin—an erythropoietic stimulating factor has been isolated from one patient.

3. *Leukemoid reactions*

Eosinophilia is noted with Hodgkin's disease and with chronic myelogenous leukemia. Increased neutrophils are again found with Hodgkins disease, and with bronchogenic carcinoma.

4. *Myelofibrosis*

Myelofibrosis, with osteosclerosis and myeloid metaplasia of the spleen may be found in breast malignancy, again without marrow involvement by tumor.

D. Thrombosis and Hemorrhage

1. *Recurrent thrombosis*

Perhaps the best known of the systemic effects of malignancy, Trousseau's sign consists of multiple, migratory superficial vein thromboses. These occur in unusual sites such as axillae, neck and upper extremities, and are resistant to anticoagulants. They may lead to gangrene of the areas (phlegmasia cerulea dolens, to be specific).

Many theories have attempted to explain this phenomenon. Pancreatic involvement has previously been considered the major offender, and the finding of increased pancreatic lipase levels and increased levels of enzymes accelerating coagulation was considered the underlying cause of the disorder. Present theories and evidence include an alteration of platelet adhesiveness, a release of thromboplastic material, increased antihemophelic globulin content, diminished fibrinloytic activity, increased antifibrinolytic activity, and a multitude of dysproteinemias. Suffice it to say that a disorder of

coagulative processes is apparent. The syndrome is found with lung, pancreatic malignancies in males, and in reproductive system, pancreatic and liver malignancies in females.

2. *Hemorrhage*

This may result from thrombocytopenia, hypofibrinogenemia, increased circulating anti-coagulants, (lysins against fibrin, prothrombin, factor V) and dysproteinemias such as cryofibrinogencmia, cryoglobulinemia. In some cases, a hemorrhagic tendency will follow an episode of thrombosis. Lesions associated are generally metastatic cancer and bronchogenic carcinoma.

3. *Purpura*

Either the enigmatic cachetic purpura, associated with wasting, chronic, and malignant disease or that due to thrombocythopenia often accompanies malignancy.

4. *Others*

Other vascular phenomena include nonbacterial, verrucal endocarditis and the carcinoid syndrome. The first, marantic endocarditis, an accumlation of fibrin on heart valves is associated in one-third of cases with mucin producing adenocarcinomas of stomach, lung and pancreas. The second is the syndrome of episodic flushing, chronic diarrhea, cardiopulmonary distress and wheezing associated with a metastatic maligant carcinoid of the liver. Other maligant tumors, all arising from foregut (lung), mid or hindgut, have been found with similar symptoms. It is postulated that these all secrete five hydroxy-tryptamine to account for the disorder. Histamine secretion has also been implicated. Not all of these tumors are found to be of the classical gut argentaffinoma type that is most commonly associated with the syndrome.

E. Neurological Disorders

Brain has classified the many signs of nervous system disease without physical involvement by the maligant process into three categories.

1. *Carcinomatous encephalomyeloneuropathy*

This is a broad classification including all the sensory and motor neuropathies found with malignancy. Pathologically a degeneration of ganglion cells is the major lesion, with or without degeneration of the long spinal tracts. Dorsal root cells are involved in sensory neuropathies, anterior horn cells and brain stem motor nuclei in mixed involvement. The signs of involvement may be those of cerebral cortical degeneration with a progressive dementia coupled with cerebellar signs. Cerebellar involvement, with loss of the cells of the dentate nuclei and fibers of the superior cerebellar peduncles will result in the dystonias commonly seen in any cerebellar deficiency. One-half of patients with these signs will have pyramidal tract signs as well.

The peripheral neuropathies may be of sensory or mixed motor-sensory types. Severe paresthesiae, limb pains, sensory loss, and motor paresis are seen—the most typical lesion the foot drop and sensory deficit in patients with bronchogenic carcinoma.

Malignancies associated with these signs may not manifest themselves until up to three years following neurological involvement. Carcinoma of the lung is the most commonly found neoplasm in this group. One study showed 16% of males with bronchial carcinoma to have peripheral neuropathy. Breast, ovary, and uterine malignancies are less frequent offenders. The same study revealed 4.4% of female breast carcinoma patients with similar symptoms. Patients without malignancy had a 1 to 2% frequency of involvement.

2. *Myopathic-Myasthenia*

When coupled with myasthenia, a syndrome of proximal muscle weakness and wasting, areas of muscle atrophy and necrosis is the common picture. Clinically there is a poor response to neostigmine injection, and a sensitivity to curare. Muscle power is noted to increase slightly on exercise, deep tendon reflexes are decreased or absent. Peripheral paresthesiae may be associated. This syndrome is found with small-cell bronchogenic carcinoma, and in 85% of cases is not the myasthenia of thymic tumor.

Myasthenia gravis associated with thymic malignancy should probably be included in the category, and differentiated from the foregoing. The clinical picture is clear, with no maximal muscle weakness, decreasing power on exercise, normal tendon reflexes. The electro-myographic studies reveal normal action potential, decreasing after stimulation or exercise, while in the myasthenia-like syndrome action potential of muscle is reduced following single stimulus of nerve, increased after brief exercise.

3. *Multifocal leukoencephalopathy*

This is a progressive syndrome resulting in hemiparesis, dementia, and impaired vision due to visual pathway interruption. Pathologically, cells in all cortical regions reveal a constant eosinophilic intranuclear inclusion of unexplained nature. The syndrome is found with Hodgkin's disease, leukemia, and lymphosarcoma, as well as in some nonmalignant conditions—tuberculosis and sarcoid.

4. *Ataxia-telangectasia*

A final syndrome, not discussed by Brain, is ataxia-telangectasia. This syndrome, associated with malignancy and with nonmalignant immunologic disturbances, couples neurological involvement with epidermal telangectasia. A number of studies postulate the lack of a component required for development or maintenance of normal immunologic systems. The reticuloses are the most commonly associated malignan-

cies, a fact leading only to further questions as to the nature of the damage done to immunologic systems.

F. Metabolic Disorders

Much attention has recently been focussed on the metabolic abnormalities associated with malignant disease. These have been characterized in the main as the known endocrine effects of nonendocrine tumors, and will be briefly reviewed.

1. *Glucose metabolism*

Both hyperglycemia and hypoglycemia have been found in patients with malignant tumors. Hyperglycemia, in the form of a diabetic glucose tolerance curve, or overt diabetes has been found in 30% of a large series of patients with malignant disease. While endometrial carcinoma is ordinarily considered the common malignancy revealing this change, bronchogenic carcinoma has been implicated in a number of series. An adult onset of unstable diabetes without family history may lead to a diagnosis of a poorly understood pancreatic neoplasm, for 15 to 20% of patients with carcinoma of the pancreas will present with that symptom.

Hypoglycemia has been studied more fully as a metabolic abnormality. Most of these derangements due to malignant or benign neoplasm are the result of functioning islet cell tumors of the pancreas. However, a formidable list of extrapancreatic lesions has been uncovered in investigation of hypoglycemia attacks. 50% of these have been the result of mesothelial tumors — retroperitoneal fibrosarcoma the most common. Hepatic carcinoma is the next most common tumor, with cases of adrenal cortical, caecal tumors, and pseudomyxoma peritonei discovered as well. Extensive metabolic studies reveal a noninsulin, hypoglycemic factor to be liberated by these tumors.

2. *Cushing's Syndrome*

As noted previously, this is the prototype lesion in the study of endocrine effects of nonendocrine tumors. The syndrome develops rapidly, often resulting in severe electrolyte disturbances before the stigmata of the disease appear. But many cases will reveal full, florid signs and symptoms, such as trunk and face obesity, hypertension, osteoporosis, alopecia, skin changes, sexual disturbances, hirsutism, thirst, polyuria and weakness. Four postulated mechanisms have been investigated. These are a hyperfunction caused by adrenal metastases, b) secretion of a steroid-like substance c) stimulation of the pituitary and d) secretion of an ACTH-like substance. Major evidence to this date reveals an increased amount of circulating ACTH-like material, with a decrease of pituitary ACTH. Apparent tumor production of this material, causing increased adrenal output of cortisol, has suppressed pituitary ACTH production. Urinary excretion of 17-hydroxysteroids is ordinarily higher than that of pituitary Cushings disease as is 17-ketosteroid excretion. Dexamethasone will not suppress urinary steroid excretion in these cases.

The associated malignancy in 80% of cases has been an anaplastic, oat cell carcinoma of the bronchus. Other lesions have been found in the thyroid, ovary, central nervous system, kidney, testis and prostate.

3. *Antidiuresis*

A number of cases of inappropriate antidiuresis (water retention and intoxication) has been noted with central nervous system and bronchogenic malignancies. In two of these an extract of an ADH-like substance has been made from the tumor itself.

4. *Hypercalcemia*

In many cases of malignancy, involvement of bone by lytic metastases will result in serious hypercalcemia and hypercalcuria. However, in a number of situations the symptoms of the metabolic upset will be present without bony metastases. The full range of symptoms—anorexia, nausea, vomiting, constipation, thirst, nocturia, polyuria, blurring of vision, lethargy, weakness—can be found with as many as 9% of malignant diseases studied. In the main, lesions of breast, lung and kidney are responsible. Recent studies have resulted in extraction from some of these lesions sufficient parathormone-like material to account for the syndrome. Nonetheless, in other cases, such as in associated leukemia, the causative agent is more difficult to elucidate.

5. *Protein disturbances*

Many abnormalities of protein structure and amount are found in these diseases. Commonly, as in many wasting diseases, a decreased serum albumin and increased alpha-2-globulin will be noted. In other cases, increased plasma mucoproteins will be detected. Macroglobulinemia, resulting in increased blood viscosity, retinopathy, bleeding diathesis, and neurologic symptons has been found in lymphocytoid malignancies. Prostatic cancer may result in cryofibrinogenemia, other lesions in the presence of cold agglutinins, cryoglobulinemia. These abnormalities may have some effect on the variability of response to infection exhibited by the patient with malignancy. A further evidence of this abnormality is the delayed host rejection of tissue transplants studied in Hodgkin's disease.

6. *Hyperthyroidism*

An interesting rarity, symptoms of hyperthyroidism coupled with increased TSH-like substances in the circulation have been found in tumors of the testis and the trophoblast.

7. *Gynecomastia*

This condition has been found as the only presenting sympton in occult bronchogenic carcinoma and

in hepatoma. The derangement of estrogen metabolism has also been found in other wasting diseases, with no clear pathogenesis in either situation.

G. Gastrointestinal Disorders

The major complication considered under this heading is that of the *Strom-Zollinger-Ellison syndrome*. The result of a definite, functioning non-beta-cell islet cell tumor of the pancreas (50% showing malignant features), the clinical picture is well known. Its main manifestations are due to increased gastrin secretion by the tumor resulting in a severe ulcer diathesis, with associated watery diarrhea, marked hypokalemia, and a malabsorption sydnrome. This last is apparently due to the inactivation of pancreatic enzymes as a result of the gross overacidity of the duodenum and jejunum.

It is felt by some researchers that this syndrome is part of a more generalized condition and hyperplasia and adenoma formation of glandular tissue throughout the body. Studies of this condition, multiple endocrine adenomatosis, have revealed varying degrees of function in all endocrine organs involved, with 20% of patients showing pituitary, parathyroid, adrenal, and beta cell pancreatic tumors. In general, this syndrome tends to be a familial, non malignant condition.

Other conditions which should be noted here will include the severe dehydration and electrolyte loss of villous adenomas of the sigmoid, and increased peptic ulcer formation in patients with bronchogenic carcinoma.

H. Genitourinary Disorders

Again not strictly due to endocrine effects, a number of geniturinary problems will be encountered in malignancies. Uric acid nephropathy has been found in acute leukemia, probably due to the increased metabolic activity of the haemotpoietic system with resultant increased nucleotide turnover.

Renal damage in multiple myeloma is another atypical situation. While myeloma cells may invade the kidney and interfere with function, this apparently occurs with extreme rarity. Renal damage is more commonly due to an alteration of glomerular permeability allowing precipitation of Bence-Jones protein intralumenally, and an obstructive, foreign body reaction to these concretions. Hypercalcemia, due to bony involvement, is the cause of damage in 30 to 60% of these cases. And in a final 10% infiltration by paramyloid is the underlying abnormality.

Priapism is at times associated with malignant disease. It is considered due to the sludging effects of leukemia cells in the cavernous sinuses, and has been found in 1% of leukemic males.

I. Infections and fever

A common systemic difficulty is the abnormal, bizarre infections which patients suffering from malignant disease will fall prey to. Host resistance to infection is deranged, both due to immunlogic globulin abnormalities, and perhaps to decreased anti-phagocytic activity of neutrophils. Antibody response mechanisms do not follow normal patterns, but the underlying difficulties are not well understood.

The fever seen with some malignancies will be of infectious origin, and a careful search for foci of infection must be carried out. Necrosis of a large tumor mass will cause fever as well. However in many cases, neither of these situations applies, and further mechanisms are postulated. Pyrogens from granulocytes, from tumors such as hypernephroma, lymphoblastoma, and Ewing's sarcoma have been investigated, without final proof of origin.

DISCUSSION

It is evident that a multitude of systemic diseases can result from unrelated malignancies. In some, a definite secretion of materials by tissue normally nonfunctioning has been demonstrated. But in many more, the changes leading to abnormality have not been elucidated, and no definite etiology is understood. In neither of these situations, however, is the pathogenesis of the lesion much more than a hypothesis. One view is presented by Green, discussing the immunologic concept of cancer. He suggests that patients with cancer, and with disease outside the cancer site of a possible autoimmune etiology have an auto immune disease tendency in general. In some of these, malignant change will result if the autoimmune disease destroys the tissue specific antigen at the tumor site, or in any way modifies the specifity of the same antigen. While this theory may relate the autoimmune phenomena to malignancy (hemolytic disease, dermatomyositis, for example), it does little to clarify the other pictures which have been discussed.

In these, it appears probable that the anaplastic, multi-potential nature of the cells involved, (anaplastic bronchogenic carcinoma) will reveal the nature of the disturbance. If cellular determination can be changed, and a specific cell type result from an apparently embryonic-like cell of another origin, the syndromes annotated can be explained—but, as yet, not understood.

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Abstracts

Therapeutic versus Prophylactic Castration in Breast Cancer

Kennedy, B. J., Mielke, P. W., Fortuny, I. E.: Postgrad. Med. 36: 310-313, Oct. 1964.

A retrospective study of results obtained on patients with breast cancer: 79 who underwent "prophylactic" castration (ovarian ablation at the time of mastectomy) and 96 who had "therapeutic" castrations (performed when cancer recurred). The patients were homogeneous with respect to age, site of the primary lesion, menstrual status, incidence of pregnancy, technique of castration and an equal distribution of tumors in stages I and II.

The interval between initial therapy and cancer recurrance was much longer in the prophylactic group showing the benefits of castration in delaying recurrance. But once the cancer reappeared in this group, survival was short. Longer survivals in the therapeutic group show the favorable effects of castration on metastatic disease. Thus, there is no significant difference in total survival time between prophylactic and therapeutic castration.

M.T.

Nonunion of the Shafts of Long Bones

Boyd, H. B.: Postgrad. Med. 36: 315-320, Oct. 1964.

Mechanization and high speed transportation have resulted in more frequent and more severe trauma with increasing predispositions to nonunion. Infection is the worst enemy to bone healing and this may be avoided by thorough surgical cleansing, immediate treatment of open fractures, closed reduction whenever possible, good soft tissue coverage, adequate fixation and avoidance of distraction by plates, screws or excessive traction.

94% of the patients reviewed with nonunion eventually healed following bone grafts. Several methods are available, some combining internal fixation and bone grafts, but no single method is best. The operation must accomplish contact, fixation, osteogenesis and compression. Osteogenesis is better stimulated by autogenous grafts than banked homogeneous frozen bone.

In spite of excellent results with bone grafting, reductions in incidence of nonunion by optimal care of acute fracturers must still be the primary goal.

M.T.

Intrauterine Transfusion for Hemolytic Disease of the Newborn

Holman, C. A., Karnicki, J.: Brit. Med. J. 2: 594-597, Sept. 1964.

Amniocentesis and spectrophotometric examination of amniotic fluid were performed on antenatal patients with high titre Rh antibodies. High optical densities indicated severe hemolytic disease and intraperitoneal transfusions were given to 5 suitable patients about one month before the estimated date of delivery.

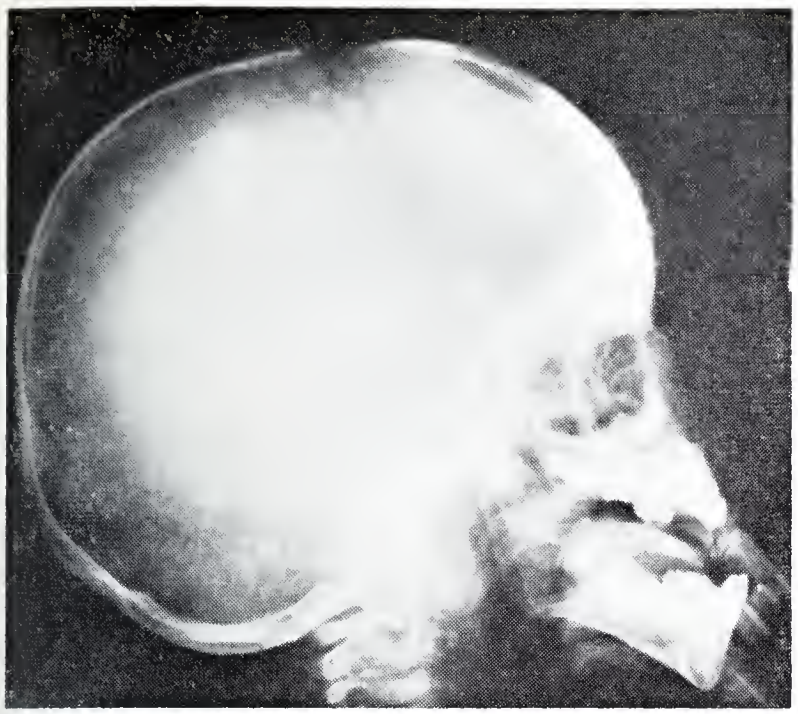
After X-ray localization of the fetus, a needle was introduced through the uterine cavity into the fetal abdomen. Urografin was injected to outline fetal abdominal contents followed by injection of 100 ml. of packed cells of the mother's type.

All 5 infants had at least one exchange transfusion after birth. One infant with hydrops fetalis could not be saved, another had his hemolytic disease controlled but died of other complications, the rest survived and are well.

Risks involved include puncture of the placenta, infection of the uterus, damage to fetal tissues and induction of premature labor.

This study shows (1) amniocentesis and spectrophotometric analysis are valuable in assessing the severity of hemolytic disease; (2) no adhesions are formed in the fetal abdomen by blood clots; (3) the blood is completely absorbed in 15 days; (4) fetal movements usually increase to normal after transfusions; (5) severe hydrops fetalis can probably be reversed by intrauterine transfusions.

M.T.



1. What group of childhood diseases may give this X-ray lesion?

On Inspection

E. M. Sellers 6T5

Malignancy in Childhood

Answers on page 84

2. This child presented with an abdominal mass. The IVP obtained indicates the diagnosis. What are the usual modes of presentation of this lesion?

3. This child presented with marked emaciation, associated with alertness and euphoria. Give a differential diagnosis. What central nervous system lesion could produce the picture seen in this child?

4. Give the differential diagnosis of the celiac syndrome. Extensive investigation revealed the cause in this child to be related to hypermotility of the gastrointestinal tract. Diagnosis?

Cancer Chemotherapy

E. P. Braaten, 6T6

INTRODUCTION

For the past two hundred years man has used drugs to combat cancer. The introduction of potassium arsenite, or Fowler's solution by Lissauer in 1865 is usually considered to be the first successful attempt at the systemic administration of a cancer chemotherapeutic agent (2). In 1898, Ehrlich, the founder of chemotherapy, discovered large doses of dimethyleneimine, an alkylating agent, caused total necrosis of renal papillae in animals. Alexander, in 1943, noted that victims of mustard gas poisoning at Bari Harbour had profound depression of leukocyte formation, and concluded that this agent might be valuable in treating neoplastic disorders of the leukopoietic tissue. The enormous strides taken in the field of biochemistry, in particular intermediary metabolism and nucleic acid chemistry, made possible a more rational approach in selecting antitumor agents. Antagonists to compounds essential in the formation of DNA and RNA were developed with the knowledge that the tumor cell, with its frequently more rapid cell division rate, would be affected most. In 1948 Farber achieved ten remissions in sixteen children with acute leukemia with the folic acid antagonist, aminopterin. In 1953 Burchenal obtained a favourable effect with the purine antagonist, 6-mercaptopurine, in patients with actue myelocytic leukemia. Hormones have been used in the treatment of cancer since the middle nineteenth century when orchiectomy was done for carcinoma of the prostate. The steroid hormones, because of their lympholytic properties, have found wide application in cancer therapy. A vast research programme is continuing today as thousands of agents are being screened for their effectiveness against various neoplasms.

The steps in the development of a new drug follow a pattern much like that of life itself. It begins with the conception of a new drug. This may be accidental or found during the routine screening of soil samples or plant leaves. The next stage is the gestation period in which the drug, in its embryonic state, is first administered to different species of animals in order to determine its toxic effects, its routes and doses of administration as well as its therapeutic effects. The birth of a drug constitutes various clinical trials. A small initial dose is gradually increased until a therapeutic result is obtained, or a toxic effect is noted, or a maximal practical dose is achieved. The drug passes through infancy and childhood when it is offered for use to qualified experienced clinicians who have proper facilities. At this stage, the drug is further evaluated and compared with other drugs. Adolescence is reached when the drug is subjected to wide distribution through the medical profession, and further information is learned about its side effects as physicians fail to regulate the dose as carefully as in the previous two stages. Finally, the drug comes of age as it reaches the market, and forms another medical instrument in the struggle against disease (4). No wonder drug has been discovered which will afford a cure for the cancer patient, but the palliation of his disease makes the agents discovered thus far worth using.

Drugs are now being administered: *systemically*, alone or combined with one or more other agents, in *conjunction with radiation and surgery*, and *locally*, via arterial perfusion to avoid systemic toxic effects.

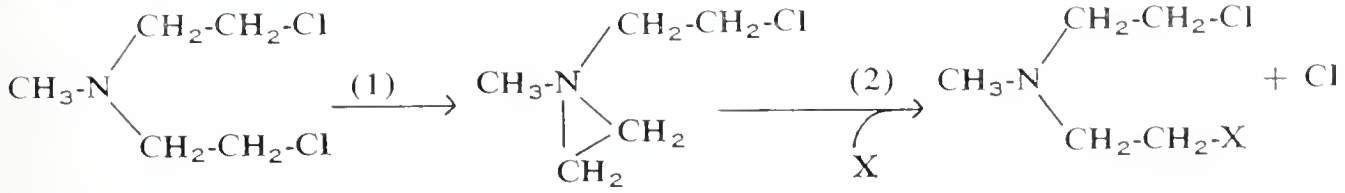
Certain concepts concerning cancer chemotherapy should be appreciated fully before undergoing a detailed study of the different agents. It is the *aim* of cancer chemotherapy to exploit the difference between the normal and maligant cell (2). We appreciate that certain biochemical differences do exist between these cells, but as yet a truly significant variation has not been found. An important problem to understand is the *resistence* which the host develops towards some drugs. An individual who has obtained a complete remission from his disease, while taking a certain agent, commonly relapses, and shows no further benefit from his treatment.

The agents to be discussed can be classified according to their mode of action; thereby, grouping themselves into the following categories: the alkylating compounds, antimetabolites, antibiotics, chemicals, and miscellaneous compounds.

ALKYLATING COMPOUNDS

Alkylating compounds are thought to act by combining with important nucleophilic groups in the cell and rendering them inactive. They are sometimes called radiomimetic agents because they cause morphological changes similar to radiation; that is the chromosomes are fragmented, inverted or deleted. Nitrogen mustard, a typical drug in this group of compounds serves to illustrate the mechanism of action of the alkylating agents. This mechanism can be broken down into two steps:

(1) the chlorethyl group is transformed into a cyclical ethyleneimine giving rise to a reactive centre at the ethyl moiety.



(2) this centre reacts with nucleophilic groups (amino, sulphydryl) and with anions of organic acids = (X).

It has been suggested that the damage occurs in the DNA molecule perhaps by breaking the hydrogen bonding between the bases, thereby rendering DNA useless to the cell. Alkylating agents may be monofunctional or polyfunctional, that is they have one or more reactive centers. Nitrogen mustard with two reactive centers can bind more firmly the important cell groupings, and indeed is fifty to one hundred times more potent than its monofunctional counterpart (2).

Before entering into a discussion on the specific properties of the various alkylating agents, the toxicity of these compounds as a group will be considered. Since alkylating compounds combine with a portion of the DNA in the cell, they have their maximum effect on all rapidly dividing cells; consequently, the blood forming cells, and the gastrointestinal epithelium are affected in addition to the tumor tissue. The following toxicities are noted: leukopenia with possible infection, thrombocytopenia accompanied in some cases by hemorrhage, nausea and vomiting, and diarrhea. The hemaglobin does not fall because the erythrocytes have a longer life span. Leukopenia below 3000 cells/cu. mm. and thrombocytopenia below 100,000 cells/cu. mm. are criteria frequently employed to limit the dose of these drugs.

The classification of the alkylating agents is arbitrary; they will be discussed under the following: nitrogen mustard and derivatives, ethyleneimines, and methanesulphonates.

Nitrogen Mustard and Derivatives:

a) *Nitrogen Mustard (mechlorethamine hydrochloride, HN2)*

Nitrogen mustard is often used as a standard of comparison for the newer mustard substitutes and other alkylating agents. Initially 0.4 mg/Kgm is given intravenously in one or divided doses, and this is repeated in 4-6 weeks. In may also be administered into body cavities to control effusions, intra-arterially for some solid carcinomas, and by isolated perfusion technique for cases in which the tumor is to be isolated from the systemic circulation. This latter technique provides a greater dose to the tumor site while minimizing the systemic toxic effects. Nitrogen mustard is used mainly in treating malignant lymphomas. 80% of patients with Hodgkin's disease have an objective response which may last several weeks to a year; however, the average response continues for 2-6 months. Objective responses with lymphosarcoma are unpredictable, but in a given series as many as 50% may show objective improvement. In these lymphomas remissions may appear within 24 hours of administering the drug. Remissions have also been achieved in patients with bronchogenic carcinoma and mycosis fungoides. The toxic effects are those common to all alkylating agents plus local symptoms of pain and thrombophlebitis if the drug is injected interstitially. Chlorpromazine and sodium amytal, administered prior to the injection of nitrogen mustard, have been useful in reducing nausea and vomiting. Weisenberger noted that the administration of cysteine to rabbits, before the injection of nitrogen mustard, resulted in the protection against leukopenia(2), and Field noticed that in mice nitrogen mustard intoxication could be reversed by antihistamines(5). Neither cysteine nor antihistamines are used clinically.

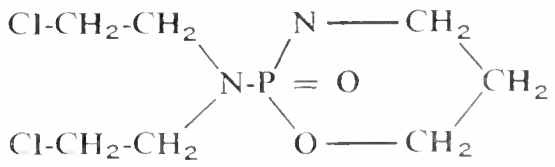
Several mustard derivatives have been developed in an attempt to enhance the destruction of tumor tissue, and to lower the toxic effects of the drug.

b) *Chlorambucil (CB 1348, Leukeran)*

Chlorambucil is a phenylbutyric acid substituted mustard which has the advantage of being administered orally. The initial dose is 0.1-0.2 mg/Kgm of body weight/day or 7-14 mg/day over 4-8 weeks. The maintenance dose is 2-4 mg./day while the patient is free of symptoms. Sometimes 0.12 mg/Kgm/day is given initially and then maintained at this level as long as improvement continues, but diminshed when the leukocytes fall below 3000/ cu. mm. Chlorambucil has found maximum use in the treatment of chronic lymphatic leukemia, lymphosarcoma and giant follicle lymphoma. Improvement usually appears within 3-4 weeks with a maximum regression within 2-3 months perhaps lasting for years. Chlorambucil is far less toxic than nitrogen mustard, but still produces leukopenia, thrombocytopenia, and some nausea and vomiting.

c) *Cyclophosphamide (Procytox, Cytoxan, Endoxan)*

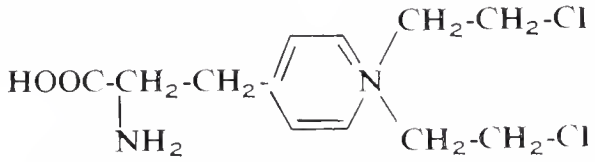
Cyclophosphamide is a cyclic phosphodiamidine in which the activity of the mustard is altered by the presence of a phosphamidide ring.



It was synthesized by Arnold and Bourseau with the hope of being specific for tumor tissue. Some tumor cells have a high content of phosphamidase enzyme, which will hydrolyse the compound releasing the active component which some think may be nitrogen mustard and others feel may be a cytoxyl alcohol. The usual dose is 2.5-3 mg/Kgm of body weight or about 200 mg/day. It is most frequently administered orally and intravenously, but is sometimes given intrapleurally. A review of the literature shows objective responses in 20 of 45 cases with Hodgkin's disease, 16 of 39 cases with lymphocytic lymphosarcoma, 12 of 23 cases with lymphoblastic lyphosarcoma, 13 of 25 cases with reticulum cell sarcoma, and 12 of 22 cases with carcinoma of the ovary. Some objective responses have also been seen in patients with carcinoma of the breast. Cyclophosphamide is less toxic than nitrogen mustard. The platelets are not depressed; and this may be due to the fact that their precursor, the megakaryocyte, is low in the enzyme phosphamidase. Leukopenia, nausea and vomiting are also reduced. Loss of hair or alopecia sometimes commences two to three weeks after therapy; however, it is only a transient phenomenon and regrowth usually occurs after the drug is stopped.

d) *Phenylalanine mustard (Melphalan, Alkeran)*

This amino acid derivative of nitrogen mustard has the formula,

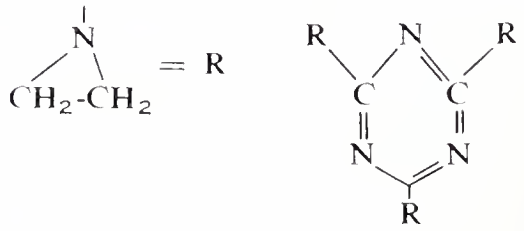


and is administered orally in a dose of 1-2 mg/Kgm in 4 days. This course is repeated at 4-6 week intervals depending on marrow recovery. Arterial perfusion techniques with melanocarcinoma have also been tried. This drug is considered by some to be the treatment of choice for patients with multiple myeloma. In the Southwest Cancer Chemotherapy Study Group a total of 196 patients with multiple myeloma have been treated with Melphalan. Of the 132 evaluable patients objective improvement was seen in 54%. In addition, there has been a suggestion that survival is prolonged. Improvement in at least two of the following parameters constituted an objective response: a shrinkage of palpable plasma cell tumors, a reduced marrow plasmacytosis, a fall in abnormal serum globulin, no proteinuria or reduced Bence Jones protein, and a rise in hemaglobin and a fall in blood urea nitrogen. Toxic effects are leukopenia, thrombocytopenia, nausea and vomiting.

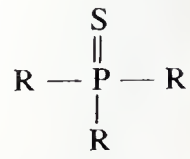
The three mustard derivatives mentioned above have found the most clinical success; other substitutes mentioned in the literature are: azo mustard, nitromin, nitrogen mustard oxide, and manitol mustard.

ETHYLENEIMINES:

An ethyleneimine is the product of the first of the two steps previously described in the mode of action of nitrogen mustard. The formulae of two of these compounds commonly called TEM and ThioTEPA may be written simply as follows:



TEM



ThioTEPA

The reactive ethyl moiety combines with the nucleophilic groups in the cell.

a) *Triethylene melamine (TEM)*

TEM, a compound synthesized in Germany as a cross-linking agent for the textile industry, seemed a logical choice to introduce into cancer chemotherapy in an attempt to cross-link chromosomal fibers of the rapidly dividing tumor cells. It may be administered orally, intramuscularly or intravenously, but is usually given orally in the dose of 2.5-5 mg./day. Sodium bicarbonate is included with the oral preparation in order to prevent its polymerization in gastric acid (2). The onset of action occurs in 1-2 weeks, but one should wait 6 weeks before concluding an inadequate response. Remissions have been obtained in various lymphomas, chronic lymphatic leukemia, and ovarian papillary cystadenocarcinoma. Marked variation in dosage effect is the chief deterrant to its use. Toxic effects are pancytopenia, and nausea and vomiting.

b) *Triethylene thiophosphoramide (ThioTEPA)*

ThioTEPA has a sulphur group replacing the oxygen of TEPA which gives the compound a greater stability in solution. It is usually administered intramuscularly or intravenously in doses of 15-30 mg/week; however it may be given into body cavities, 30-60 mg/week, and directly into tumor tissue. It has found frequent use in late stages of carcinoma of the breast and the ovary which have seeded the pleural and peritoneal surfaces respectively. Lyons obtained an 8 month mean remission for pleural metastases and a 60% response rate in the reduction of ascites due to peritoneal metastases (6). Remissions have also been obtained in cases with chronic leukemia and malignant lymphomas. The toxic effects, with the addition of mental depression, are similar to triethylene melamine.

METHANESULPHONATES:

Busulphan (Myeleran)

Busulphan is the only drug worth mentioning in this group. Its active components are the ester groups, $R\text{-}SO_2\text{-}O\text{-}R_1$, which can be found in its formula, $CH_3\text{-}SO_2\text{-}O\text{-}(CH_2)_4\text{-}O\text{-}SO_2\text{-}CH_3$. It is administered orally, and the preferred dose is 4 mg/day until the

leukocytes fall to 20,000. The maintenance dose is 2 mg./day. Galton and his co-workers showed a selective action of myeleran on myeloid tissues, and then established its use in chronic myelogenous leukemia (1). It is now considered to be the drug of choice in this disease; however, it has not been shown to be significantly better than splenic irradiation. Studies comparing radiation to the spleen and myeleran are being carried out at the present time. Optimum benefit from treatment is achieved 2 months after the administration of the drug, and remissions may last from 1-3 years. As with other cancer chemotherapeutic agents life has not been prolonged significantly; nevertheless, definite palliaition throughout the course of the disease is observed. The main side effect is bone marrow depression, and the cells affected in order of sensitivity are the granulocytes, platelets, and erythrocytes. Other toxic effects are permanent amenorrhea, hyperpigmentation of the skin in women, and gynecomastia in men.

ANTIMETABOLITES

Antimetabolites are substances which structurally resemble vitamins, coenzymes, or normal intermediary metabolic products, but differ enough to compete with them in essential metabolic processes. They are thought to act during DNA synthesis in the S phase of the cell cycle. The metabolites most frequently opposed are: folic acid, purines, and pyrimidines. These compounds are found in normal tissue as well as tumor tissue; thus, in the process of treatment, normal healthy tissue is also destroyed. Attempts to isolate a metabolite unique to tumor tissue, for example, vitamin B, and certain amino acids, have been unrewarding.

Folic Acid Antagonists:

Folic acid antagonists combine with the enzyme folic acid reductase, and prevent the conversion of folic acid to tetra-hydrofolic acid. This interferes with the action of folic acid, namely, the transfer of methyl groups in the synthesis of thymidylic acid of DNA. Amethopterin, a methyl derivative of aminopterin, is the major folic acid antagonist in use at the present time. It is administered most commonly by mouth, but occasionally it is given intramuscularly or intravenously. Its chief use is in acute leukemia in children where, with a dose of 0.1-0.2 mg/Kgm/day, remissions appear in about 60% of cases. Responses occur in about 2-3 weeks and have a median duration of about 8 months. Adults with acute leukemia seldom respond; however, adults with choriocarcinoma achieve an objective response in 50% of cases using 25 mg intramuscularly daily for 5 days in repeated courses at 4-6 week intervals as tolerated. 2.5-5 mg are given by mouth, each day in adults with various lymphomas and sarcomas, and larger doses or 25-50 mg. daily are given, by the arterial perfusion technique, in squamous cell carcinomas of the head and neck. At the same time as the perfusion, citrovorum factor is injected intramuscularly. Untoward effects are depression of bone marrow, stomatitis, hyperpigmentation, alopecia, diarrhea and dermatitis. Congenital malformations, hydrocephalus and hair lip, are apt to occur if these agents are given during the first trimester. These toxic effects can be reversed by folinic acid (citrovorum factor) if given after 1-2 hours.

Purine Antagonists:

Hall (2) classifies the purine antagonists into two groups, the "antipurines" and the "purine analogues". The antipurines are those agents which interfere with the synthesis of the purine ring, for example DON and azaserine; the purine analogues are those drugs which interfere with the incorporation of purines into nucleic acids, for example 6-mercaptopurine.

a) *Azaserine*

The antibiotic azaserine, which is administered in doses of 8-10 mg/day either intravenously or orally, has found limited clinical use. It reduced fever in Hodgkin's disease, and was found to give a brief remission in some other neoplastic processes. The toxicity is mainly gastrointestinal in naure, for example redness of the tongue, stomatitis, nausea and vomiting, but azaserine also causes bone marrow depression.

b) *6-Mercaptopurine (6MP)*

6-mercaptopurine interferes with the incorporation of hypoxanthine into DNA or may be incorporated into DNA itself. It is the only purine analogue which has found lasting clinical use, and is administered orally in the dose of 2.5 mg/Kgm per day. As with Methotrexate, its major use is in the treatment of children with acute leukemia, and in these cases 60% achieve a remission after 2-6 weeks of therapy. Therapy should be continued during the period of remission. 6MP is less effective in adult acute leukemia; nevertheless, it is still the drug of choice in this disease. 20-25% of these patients obtain an objective response which, unfortunately, is of a rather short duration. The toxic effects are marrow depression, ulceration of the G.I. mucosa with ensuing diarrhea, nausea and vomiting, and in some cases hepatic necrosis.

Pyrimidine Antagonists:

Few pyrimidine analogues showed any striking tumor inhibition until the discovery of Duschinsky and Heidelberger of a new group of 5-fluoropyrimidines in which 5-fluorouracil, 5 FU, was one of the effective agents (1). 5-fluorouracil is incorporated into ribonucleic acid; however, its lethal effect appears to be related to the inhibition of thymidylate synthetase, thus blocking the formation of thymidylic acid. 5 FU is administered intravenously in the dose of 15 mg/Kgm/day, not exceeding 1 gm./day, for 5 days followed by 7.5 mg/Kgm

on alternate days until toxicity occurs. Repeated courses may be given at 4-6 week intervals. This drug gives effective palliation in far advanced cancers incurable by standard surgical and radiological techniques. A review of the literature shows the range of responses in different series: carcinoma of the breast, 30-56%, carcinoma of the colon, 16-35%, carcinoma of the stomach, 18-25%, and cacinoma of the ovary, 19-57%. The duration of response is usually short; averaging from 2-6 months. The major disadvantage of 5 FU is its severe toxicity; consequently, one must weigh the benefits of the treatment against the possible side effects of the drug. The toxic effects are: pancytopenia, stomatitis, nausea and vomiting and alopecia.

ANTIBIOTICS

Thousands of antibiotics are screened each year for specific antitumor action, and at least 25 have reached clinical trials, but because of their high toxicity, very few have been incorporated into the field of useful cancer chemotherapeutic agents.

Actinomycins:

The actinomycins are bright red in colour because they are composed of a red chromophore linked to a polypeptide chain. They interfere with DNA to the extent of preventing messenger RNA formation. Actinomycin C is administered intravenously in the dose of 400 mg/day for as many as 25 days. It has been used with minimal effect in patients with lymphomatous disease, although some success with Hodgkin's disease has been reported. Actinomycin D was discovered by Waksman and Woodruff in 1940, and Farber, in 1955, demonstrated a carcinolytic action against transplanted mouse tumors, for example malignant melanoma, mammary adenocarcinoma, and myeloid and lymphatic leukemias(3). In adults this drug is administered intravenously in the dose of 0.5 mg daily for 5 days; whereas, in children one gives 0.075 mg/Kgm divided into 5 equal daily injections. In children, favourable results have been obtained in tumors of mesodermal origin, and especially in Wilm's tumor of the kidney. Some feel, that in these cases, the addition of radiation to the Actinomycin regime prolongs the survival of these children. In the solid tumors of adults Actinomycin shows little effect. It has been administered with Chlorambucil and Methotrexate, so-called triple therapy, in the management of testicular tumors, but little objective response was achieved. Some lymphomas and rhabdomyosarcomas have responded briefly to Actinomycin D. The untoward effects are noticed, in the main, on the bone marrow, gastrointestinal tract, and skin (rash, alopecia).

Mitomycin:

Mitomycin is an antibiotic isolated from Streptomycetes caespitosus, and has found use in some solid tumors, but has limited application because of its severe toxic effects.

CHEMICALS

Over the years many chemicals have been utilized in attempts to treat cancer; three of the more interesting agents will be discussed.

a) *Fowler's solution (Potassium arsenite)*

Fowler's solution, as mentioned previously, has historical significance. In 1865, it was used by Lissauer in a case of leukemia because of an alleged benefit on the appetite and coat of a sick horse. It has been used very rarely in the treatment of chronic myelogenous leukemia. The usual dose is 5 minims three times a day; this dose is gradually increased to the tolerance level of the individual at which time nausea and vomiting occur.

b) *Urethane (Ethyl carbamate)*

Urethane, C_2H_5-O-CO-NH_2, was shown by Haddow and Sexton to be an active agent against the Walker rat carcinoma (3), and subsequently, has found some clinical application in multiple myeloma. It is administered orally in doses ranging from 1 to 5 grams per day until a total does of 100 grams is reached. Experience has found it to be poorly tolerated in doses over 1 gram per day, and consequently nausea and vomiting, anorexia, and marrow depression markedly limit its use.

c) *Colchicine & derivatives*

Colchicine and its derivatives are natural alkaloids derived from the autumn crocus. Colchicine was used for the treatment of gout as early as the 6th century, and still finds its main use in treating the acute form of this disease. It acts by inducing an arrest of the metaphase during cell mitosis. Demicolcine, was found to inhibit granulopoiesis, and thus has been given to patients with chonic myelogenous leukemia. It is preferred to colchicine because it is less toxic; although granulocytopenia, alopecia, skin rashes, cholestatic jaundice, and the inhibition of spermatogenesis may occur with its use. Demicolcine is given orally in the dose of 5 mg per day, and may be raised to 10 mg per day until the WBCs drop to 30,000/ cu. mm. when the dose should be decreased to 1-4 mg per day.

MISCELLANEOUS

The miscellaneous group could extend on for many pages; however, it will be restricted to include the hormones, the vinca alkaloids, bacterial toxins & oncolytic viruses, and a brief mention of cancer immunity.

Hormones:

Some would question the inclusion of the hormones in a discussion on cancer chemotherapy; however, their omission would constitute an even greater error. As with the chemotherapeutic agents, the hormones are used in the more advanced cases of cancer.

a) *Glucocorticoids*

Prednisone and similar glucocorticoids have found wide use in the treatment of the leukemias and the malignant lymphomas. Prednisone when given in a dose of 2 mg/Kgm/day has the ability to induce a quick remission in children with an acute fulminating leukemia. These remissions may be short; however, one can then employ an antimetabolite to achieve a further remission. In adults 40-60 mg/day, given by mouth in 4 divided doses, has been useful in treating a few cases of acute leukemia, some cases of chronic lymphatic leukemia and lymphosarcoma. Carcinomas of the breast, and acquired hemolytic anemias, which occur in various neoplasms, have shown beneficial responses when treated with glucocorticoids.

b) *Sex hormones*

Since the sex hormones are so intimately related with the development of the primary and secondary sex characteristics, it was only natural that the manipulation of these compounds in the treatment of neoplasms of the "reproductive organs" would be attempted. In treating carcinoma of the prostate, one may lower androgen levels by bilateral orchiectomy or one may administer orally 5 gm of diethylstilbestrol three times a day. With androgen ablative therapy in carcinoma of the prostate, symptomatic relief of bone pain and improvement of appetite are noticed along with signs of weight gain, a rise in hemaglobin, a decrease in serum acid phosphatase, and a decrease in tumor size (3). Androgens are also of some value in treating carcinoma of the breast, and in this disease 50-100 mg of testosterone proprionate are administered three times each week. When treating women with testosterone, one must remember the masculinizing complications which may occur, for example, virilism, hirsuitism, deepening of the voice, and acne.

Estrogens are widely used in far-advanced cancer of the breast in women well past the menopause. It is postulated that the reduction in natural female estrogens induces an uncontrolled proliferation of the epithelial cells of the breast, and it is believed that one can control this progression by reinstituting estrogens. Estrogens have shown a greater degree of control than androgens in treating metastatic breast carcinoma in post menopausal women. Diethylstilbestrol is the most commonly used estrogen, and it is given orally in a dose of 15 mg per day. Ablative estrogen therapy has proven most beneficial in menopausal and some premenopausal women with carcinoma of the breast; oophorectomy, adrenalectomy and hypophysectomy are the methods employed.

More recently progesterone has been shown to be useful in treating tumors of the body of the uterus. With this fact in mind, a dose of 100 mg. of Provera is given by intramuscular injection each day, and is continued for several months.

VINCA ALKALOIDS:

Two important antitumor agents have recently been extracted from the leaves of the plant, Vinca Rosea, commonly called the periwinkle. These are vincaleukoblastine, and vincristine sulphate.

a) *Vincaleukoblastine (Vinblastine sulphate, Velbe, VLB)*

Vinblastine sulphate is thought to inhibit rapidly dividing cells by arresting their growth in the metaphase. It is administered intravenously in the dose of 0.15-0.2 mg/Kgm/week or 10 mg/week until the white blood cell count drops to 3000/ cu. mm. Rarely, it is administered orally or into the pleural space. It is of value in Hodgkin's disease since over 50% of cases achieve an objective response which lasts 2 months or more. Some people feel it is as effective as nitrogen mustard in treating Hodgkin's disease. It may also be effective in other malignant lymphomas, choriocarcinoma, and carcinoma of the breast. The chief advantage of VLB over nitrogen mustard is its reduced toxicity. It causes leukopenia, but seems to spare the platelets and the erythrocytes; occasionally it causes nausea and vomiting, alopecia, and local pain and thrombophlebitis if it is accidently injected interstitially.

b) *Vincristine sulphate (Oncovin)*

The mode of action of Vincristine is unknown; however, in vitro it is thought to cause metaphase arrest. Being more potent than its alkaloid relative, Vinblastine, only 0.01-0.05 mg/Kgm dissolved in 10 ml of water or saline is required once or twice each week. It takes fifteen tons of dried periwinkle leaves to produce one ounce of vincristine (4).

It is usually injected either directly into a vein or into the tubing of a running intravenous infusion. Neurological signs of numbness and tingling and loss of deep tendon reflexes are indicators which limit the amount of drug given. It has found maximum use in the treatment of acute leukemia in children in a dose of 0.07-0.1 mg/Kgm intravenously weekly and some feel it has surpassed 6-mercaptopurine and amethopterin as the drug of choice in this disease. It has also found use in malignant lymphomas, and, in particular, reticulum cell sarcoma. Toxic effects are severe; they include leukopenia, anemia, neuromuscular signs, constipation, alopecia, and local pain and thrombophlebitis if injected interstitially.

BACTERIAL TOXINS & ONCOLYTIC VIRUSES:

a) *Bacterial toxins*

Patients with inoperable sarcoma showed improvement when they accidentally contracted an infection. A surgeon named Coley reasoned that the remissions in these cases were due to toxins secreted by certain bacteria; therefore, he prepared extracts of these killed

bacteria, "Coley's toxins", and injected them into appropriate patients. Some antitumor activity was noted: however, gross systemic toxicity also occured. Although the responses were not too good, the theoretical implications are very interesting. Diseases such as multiple myeloma and Hodgkin's disease, in which there is a reduction in the ability to form antibodies, may be amenable to this type of therapy (2).

b) *Oncolytic viruses*

An oncoyltic virus (once = mass, lytic = dissolution) is really an antimetabolite which competes with the formed nucleic acid in the cell. Some viruses which have been used are vaccinia, rabies, and the neurotrophic viruses. Little use is made of this technique now, probably because of the "rapid onset of immunity by the host, lack of uniform killing effect on all tumor cells, lack of predictable oncolytic activity on the part of the viruses, and inability to ensure uniform infection in all patients" (2).

CANCER IMMUNITY

This subject has been a topic of much interest and debate in the past few years. Researchers have attempted both active and passive immunity. In the former method tumor tissue is injected intravenously into the patient in an attempt to induce an immune response, the formation of antibodies against his own tumor. In the latter method antibodies, formed by injecting tumor tissue into another person or animal, are injected into the patient. Some responses have been seen, noteably in tumors of the breast and cervix; however, toxic effects are a major problem. Perhaps, as took place with bacteria, the immune mechanism will come to the foreground in the prevention and cure of some cancers.

SUMMARY

In summary, a list of some neoplastic diseases with their current drugs of choice and initial doses is presented.

Disease	Current Drug of Choice gerenic name (trade name)	Initial Dose-Route
Acute leukemia		
(a) *children*	Prednisone - quick remission	2mg/Kg/day p.o.
	1. Amethopterin (Methotrexate)	0.1-0.2 mg/Kg/day p.o.
	2. 6-Mercaptopurine (6 MP)	2.5 mg/Kg/day p.o.
	3. Vincristine sulphate (Oncovin)	0.07-0.1 mg/Kg/week i.v.
	4. Cyclophosphamide (Procytox)	2.5 mg/Kg/day p.o.
(b) *adults*	1. 6-Mercaptopurine (6 MP)	150 mg/day p.o.
	2. Prednisone	40-60 mg/day p.o.
Chronic lymphatic leukemia	1. Chlorambucil (Leukeran)	0.1-0.2 mg/Kg/day p.o.
	2. Prednisone	30 mg/day p.o.
Chronic myelogenous leukemia	1. Busulphan (Myeleran)	4 mg/day p.o.
Multiple myeloma	1. Phenylalanine mustard (Melphalan)	1-2 mg/Kg/over 4 days; p.o.
	2. Cyclophosphamide (Procytox)	2.5 mg/Kg/day p.o.
	3. Urethane	1-5 g/day p.o.
Hodgkin's disease	1. Nitrogen mustard (HN2)	0.4 mg/Kg/once only i.v.
	2. Vinblastine sulphate (VLB)	10 mg/week i.v.
Lymphosarcoma	1. Chlorambucil (Leukeran)	0.1-0.2 mg/Kg/day p.o.
	2. Prednisone	30 mg/day p.o.
Giant follicle lymphoma	Chlorambucil	0.1-0.2 mg/Kg/day p.o.
Reticulum cell sarcoma	Vincristine sulphate (Oncovin)	0.01-0.05 mg/Kg/wk. i.v.
Mycosis fungoides	1. Nitrogen mustard (HN2)	0.4 mg/Kg/ once i.v.
	2. Cyclophosphamide (Procytox)	2.5 mg/Kg/day p.o.
Carcinoma of breast		
(a) *premenopausal*	Ablative estrogen therapy	
(b) *post menopausal*	Diethylstilbestrol	15 mg/day p.o.
	5-Fluorouracil (5 FU)	15 mg/Kg/day x 5 then 7.5 mg/Kg/alternate days i.v.
(c) *pleural metastases*	Triethylene thiophosphoramide (ThioTEPA)	30-60 mg/week into pleural cavity

CANCER CHEMOTHERAPY

Disease	Current Drug of Choice gerenic name (trade name)	Initial Dose-Route
Carcinoma of prostate	Ablative androgen therapy Diethylstilbestrol	 15 mg/day p.o.
Carcinoma of ovary	Triethylene thiophosphoramide (ThioTEPA) Chlorambucil (Leukeran) Cyclophosphamide (Procytox)	15-30 mg/week i.v. 7-14 mg/day p.o. 200 mg/day p.o.; i.v.
Carcinoma of body of uterus	Progesterone (Provera)	600-700 mg/week i.m.
Gastrointestinal malignancies	5-Fluorouracil (5 FU)	15 mg/Kg/day x 5 i.v. then 7.5 mg/Kg/alternate days
Carcinoma of lung	Nitrogen mustard (HN2)	0.4 mg/Kg/ once i.v.
Carcinoma of head & neck	Amethopterin (Methotrexate)	25-50 mg/day i.a. (infusion)
Choriocarcinoma	Amethopterin (Methotrexate) Vinblastine sulphate (VLB)	25 mg/day x 5 i.m. 10 mg/week i.v.
Wilm's tumor	Actinomycin D	0.075 mg/Kg/day i.v.

CONCLUSIONS

A great deal of laboratory experimentation is being conducted in various research centers across North America, and indeed, all over the world in an attempt to discover potent antitumor drugs. Many of these centers have clinics in which controlled studies are underway which are assessing the value of the known cancer chemotherapeutic agents, and comparing their effectiveness in specific diseases with other known drugs. No doubt that with the combined efforts of these experimental and clinical workers, compounds will be discovered which will afford an increasingly greater palliation to the cancer patient.

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Exfoliative Cytology: General Considerations

L. B. Taichman 6T5

Exfoliative cytology is the diagnostic science based upon the interpretation of features which are observed in cells which have been shed or removed from the surfaces of body organs. Exfoliative cytology is not a new field, for as early as 1843 Walshe remarked upon small fragments of tissue expectorated from malignant growths of the respiratory tract. However, not until the late 1930's and 40's did George N. Papanicolaou popularize this type of investigation and demonstrate its usefulness, particularly with reference to the female genital tract.

The applications of cytology are founded upon several basic principles viz: 1) Spontaneous exfoliation of cells as a result of continuous growth of epithelial linings from which more superficially placed cells are constantly shed and replaced by younger ones. Such exfoliated cells may accumulate in various cavities, such as the vagina. 2) At one stage in carcinogenesis, specific morphological alterations appear in a single cell or groups of cells. Some of these abnormal cells will exfoliate or be removed artificially and gathered up in the samplng. The sample then contains an overall picture from a large area, and only a few characteristic cells are needed to make the diagnosis. Tissue biopsy however, covers only one or more isolated areas and requires malignant changes in groups of cells for diagnosis. 3) In the early stages of its development a malignant lesion which is evident microscopically may not yet have any changes detectable on gross examination. Cytology is ideally suited for the detection of such lesions. Indeed, in the late and grossly obvious stages of a malignant lesion, there is often ulceration, secondary inflammation, and superficial necrosis, all of which make material from the surface of the advanced lesion less dignostic. For this reason statistics indicate that approximately 98 to 100% of early malignant lesions of the cervix are detected by exfoliative cytology on direct smears, while only 60 to 70% of surface material from advanced, crusted, ulcerated, and partially necrotic lesions are diagnosed.

Cytology should be used either as a diagnostic aid which complements other means of investigation, or should be employed for the detection of lesions which would not be discovered by other means. Cytologic examination is relatively inexpensive, and in most situations is an easy procedure which is feasible for the practitioner's office. The availability of interpretation of such specimens is now quite general.

The details of cellular structure and alterations which are observed in cytologic preparations are not the subject of this discussion. Suffice it to say that nuclear abnormalities form the essential changes seen in smears of malignant cells. Instead, the following summary is designed to acquaint the student with the possible uses of cytology in the various organ systems and to serve as a quick reference when one is confronted with various clinical situations in which cytology may be applied. For each organ system mentioned, the samples submitted and the information obtainable from cytologic examination will be put forth, and any necessary qualifying points will be added.

FEMALE GENITAL TRACT

Vagina, cervix, endometrium, and other portions of the genital tract.

Samples Submitted

(a) *Vaginal smear.* Desquamated cells from the exocervix and vagina accumulate in the posterior fornix along with material that has flowed into the vagina from the endometrium and endocervix. This vaginal pool of material is removed, and like all other samples, is spread on a glass slide, fixed, stained, and examined microscopically. This type of smear is of particular value in cytohormonal assessment, evaluation of irradiation effects, and detection of endometrial as well as cervical lesions.

(b) *Cervical smear.* The surface of the cervix is scraped circumferentially with a spatula specifically designed for this purpose. The material obtained is the best for the assessment of cervical lesions.

(c) *Combination cervical vaginal smear.* The combination of the two types mentioned above may be submitted on a single slide. This smear is frequently used for routine cancer detection.

(d) *Endocervical aspiration.* The contents of the endocervical canal are aspirated with a cannula. A localized sample is obtained.

(e) *Endometrial aspiration.* With a special cannula and without dilatation, material may be aspirated from the endometrial cavity. However, this procedure is much less routine in its application than those listed above.

Information Provided By Cytology

1. Cancer Detection

(a) *Screening.* Screening procedures are ones used for the detection of early and unsuspected lesions in the

asymptomatie patient. With referenee to the female genital traet, a eomprehensive 12 year study in British Columbia has revealed malignancy of the eervieal epithelium in 1 out of 160 women over 20 years of age. 95% of these lesions were in the in situ (preinvasive) stage, and 91% of all positive cases had no grossly visible lesion which was diagnostic. Since this programme has assumed major proportions, the ineidence of invasive carcinoma of the cervix in women in British Columbia has been redueed by 40%.

(b) *Differential diagnosis.* Cytology is employed to help distinguish the various pathological states in the symptomatie patient.

Cervix—The technique is highly accurate for distinguishing between inflammatory lesions, benign tumors, dysplasia, and malignaney both in situ and invasive.

Endometrium—Cytology may be used to detect unsuspected cases, but dilatation and eurettage is the procedure to be followed in symptomatic eases.

Other sites—Neoplasms of the ovaries and fallopian tubes are occasionally diagnosed by cytology, but this of eourse is usually fortuitous and is not routine. Occasionally evidence of metastatie lesions from distant sites is apparent.

(e) *Detection of recurrence.* Reappearanee of a lesion after surgical or irradiation therapy may be diseovered by eytology.

2. Hormonal Studies

Vaginal epithelium is a target for ovarian hormones, and morphological changes fluctuate aecording to the nature of the hormonal state at the time. Rather speeific findings are applied to the investigation of sueh clinical problems as: ovulation and fertility studies, oligomenorrhea, assessment of the degree of ovarian function, pregnaney ehanges, abortion, effects of administration of artifieial hormones.

3. Other Information

Smears from this area yield information pertinent to vaginal infection by trichomonas and candida albicans, the response to therapy, and other information sueh as the presenee of spermatoza, ete.

RESPIRATORY TRACT

Lungs, bronehi, trachea, larynx, pharynx, posterior nasophyarynx, and mouth.

Samples Submitted

(a) *Sputum.* The deep morning cough speeimen is the ideal material—NOT saliva. In the morning the patient is often able to expeetorate the sputum which has accumulated in the lungs during the preceding hours. Multiple specimens are usually required to provide reasonably representative sampling.

(b) *Bronchial secretions.* Aspirations of mueus taken during bronchoseopy.

(c) *Bonchial Washings.* Isotonic saline may be instilled into the bronehus during bronchoseopy and then aspirated.

Information Povided By Cytology

1. Cancer Deteetion

(a) *Screening.* A projeet in Philadelphia devoted to the earliest possible detection of lung caneer by ehest x-ray at frequent intervals revealed that by the time there was radiologic evidence of lung eaneer, signifieant symptoms had been present for about two and one half years in over half of the patients. The patients who were discovered by this means did not have a significantly better prognosis than the average series of eases of lung eancer, indieating that the lesions were already relatively advaneed. Some clinies, ineluding the Toronto General Hospital, employing cytologic sereening have now deteeted several early lesions in heavy smokers who had no deteetable abnormality on x-ray. These eases have had a markedly improved prognosis when eompared with the average type of ease diseovered at a later stage.

(b) *Differential diagnosis.* Positive findings are often very helpful, but negative ones, partieularly in those cases with a peripherally placed coin lesion, are not uneommon, and in many cases multiple sampling is required before a signifieant result is obtained. It is possible to differentiate in sputum material between dysplastic ehanges and the various types of eareinoma ineluding squamous, anaplastie, and adenoeareinoma.

(c) *Detection of Recurrence.* After surgery or irradiation therapy.

2. Inflammatory States

Lipoid pneumonia, pneumoeystis, myeotie infeetion, alveolar proteinosis may all present early charaeteristic findings on cytologieal examination, but diagnosis by sueh methods is of eourse not routine.

PLEURAL AND PERITONEAL CAVITIES

Sample Submitted

The subpleural lymphaties are eommon sites for metastatie malignant growths which usually are associated with the accumulation of fluid in the pleural eavities. This fluid may eontain malignant cells exfoliated from those lesions which do involve the pleural surfaces in addition to the lymphatics. Sueh fluids may be easily aspirated by a needle. The same principles apply to the peritoneal eavity. It has been found that degenerating mesothelial eells may assume quite abnormal appearanees, and interpretation of speeimens cytologically is often more difficult than the interpretation of most other types of speeimens.

Information Provided By Cytology

1. Tumour Origin

Though the type of tumour cannot always be demonstrated clearly, it is sometimes possible to differentiate between adenocarcinoma and epidermoid carcinoma by the presence of keratin or mucus. Other very specific types such as malignant melanoma, malignant lymphoma, and primary mesothelioma may be demonstrated.

2. Prognosis

The demonstration of malignant cells in the pleural or peritoneal material is often of value in estimating a prognosis and in deciding the form of therapy.

GASTROINTESTINAL SYSTEM

ORAL CAVITY

Tongue, gingiva, buccal mucosa, etc.

Samples Submitted

Scrapings are obtained directly from the lesion. Patients are often unaware of the early lesion, and dentists are frequently reluctant to recommend biopsy of the asymptomatic lesion. Cytology offers a simple painless investigative tool for the assessment of early lesions which are equivocal.

Information Provided By Cytology

1. Cancer Detection

The benign and malignant growths may be distinguished and one may be alerted to the presence of early malignant change in leukoplakia.

2. Sex Chromatin

Buccal smears are the simplest and most widely used type of procedure for the demonstration of the presence or absence of the "Barr Body" in somatic cells.

STOMACH

Sample Submitted

It is important to realize that gastric cells, once exfoliated, are rapidly digested by the acid-pepsin mixture. Therefore, precautions such as the discarding of a fasting specimen, fresh lavage with saline, and the chilling of the samples obtained will greatly improve the results of this technique.

Information Provided By Cytology

1. Cancer Detection

Carcinoma and lymphomas may be detected in this way and this procedure is most helpful in cases in which x-ray findings are equivocal.

2. Response To Therapy

After surgery for gastric cancer, recurrence may be detected by cytological means.

COLON

Samples Submitted

Enemas using Ringer's solution or washings obtained during sigmoidoscopy.

Information Provided By Cytology

Occasionally adenocarcinomas of the large bowel may be diagnosed cytologically in the absence of definitive clinical or roentgenographic evidence. This method leaves much to be desired because of the technical problems in obtaining adequate and representative material.

OTHER PARTS OF THE GASTROINTESTINAL SYSTEM

Oesophageal, duodenal, biliary, and pancreatic samples may be studied, but usually the techniques are too elaborate and difficult to warrant use.

CENTRAL NERVOUS SYSTEM

Cerebrospinal fluid may be obtained from a lumbar puncture. The principles involved are the same as for pleural aspirates. Metastatic tumours to the brain, chord, or meninges may exfoliate into the cerebrospinal fluid and may be detected cytologically. Moderate success has been reported in the detection of primary neoplasms through the central nervous system.

UNINARY TRACT

Urethra, bladder, ureters, and renal pelves.

Sample Submitted

Urine, voided or catheterized. The urine is hypertonic and causes degenerative changes in exfoliative cells. Therefore fresh urine is the best sample. One should not expect renal parenchymal cells to be present in the urine, unless the lesion has involved the renal pelvis.

Information Provided By Cytology

1. Cancer Detection

Cytology affords a means of discovering a very early lesion or aiding in the assessment of an obvious lesion in conjunction with cystoscopy, intravenous and retrograde pyelography, etc.

2. Response To Therapy

Cytology may be a valuable means of assessing the effectiveness of treatment in a bladder which is deformed and scarred after irradiation and surgery. Transitional cell carcinoma of the urinary tract is particularly prone to recurrence or to multifocal origin, and follow-up cytology might be quite useful in this respect.

BREAST

Discharges from the non-lactating breast in which there is no obvious palpable lump should warrant cytological examination. If there is a cystic lump, biopsy is a method of choice since though cytology may be done, there is not necessarily a direct correlation between presence or absence of the cystic lesions and the presence or absence of carcinoma.

MALE GENITAL SYSTEM

Prostatic and seminal vesicle secretions can be obtained by prostatic massage, but the application of this procedure is rather limited.

CIRCULATING BLOOD

Malignant cells have been demonstrated in samples from the peripheral blood stream in 15 to 20% of cancer cases. The exact significance of such findings, particularly with reference to prognosis, it still debatable and is now being subjected to critical analysis.

SUMMARY

The results of cytologic findings are reported in various ways but all systems have three basic categories, (apart from unsatisfactory). These are positive for malignant cells, negative for malignant cells, and inconclusive. The last category may be used for samples in which there is degeneration, or technical factors do not allow precise interpretation, or there are insufficient criteria for malignancy but nevertheless abnormal cells are present. A negative result does not rule out the existence of a lesion not represented in the smear. A suspicious result merits a follow-up assessment. In any case there must be close liason between the clinician and the cytopathologist.

It is not meaningful to assess the overall reliability of cytology. Reliability varies with the origin of the sample, the adequacy of the sample, the physiological dynamics of the area in question, the presence of interfering material, the sampling technique employed, the fixing and staining procedures, the proficiency of laboratory, and the preparation and screening of material, the method of communicating results, and quite obviously upon the degree of experience of the cytologist.

The useulness of cytology has now become well established and appreciated. Theoretically invasive cancer of the cervix could be almost eradicated if cervical smears were performed routinely in every woman over 20. Pulmonary cytology, if some problems of sampling can be further overcome, may become the key to the early diagnosis of increasingly common lung cancer, a disease which is extremely lethal in the stage of development in which it has been usually discovered heretofore. Improved techniques of sampling and closer clinical cytopathological liason will set the pace for advancement in the future.

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Abstract

Hyperbilirubinemia in Breast-fed Infants

Newman, A. J., Gross, S.: Pediatrics 32: 995-1001, Dec. 1963.

A report of 11 breast-fed infants in whom hyperbilirubinemia persisted for 2-6 weeks after birth. 5 were breast-fed throughout, one was given supplements of cows milk and 5 were fed entirely on cows milk.

Decline in serum bilirubin was slowest in the breast-fed infant, most rapid in the infant with cows milk supplements and equally rapid in the others once the cows milk feedings were started. Although the authors could not demonstrate the cause of this phenomenon, they feel further investigation may reveal an inhibitor to bilirubin diglucuronide conjugation in breast milk.

M.T.

Recent Advances

Lymphangiography In Malignant Disease

Intralymphatic injection of a contrast medium in the living person began in 1930, but only in the last three years has it been developed extensively. The *technique* generally used involves the subcutaneous injection of a 0.5 ml of Patent Blue dye in 1% procaine HCL into the interdigital webs of both feet. After suitable lymphatics show through the skin, under local anaesthetic a transverse incision is made at a variable level on the dorsum of the foot. A superficial lymphatic vessel is found, stripped of fat and areolar tissue and cannulated with a narrow gauge needle (number 26-30). The needle is attached by fine polythene tubing to syringes containing a radiopaque contrast medium, Ultra Fluid Lipiodol (UFL). Lead weights mounted on the plunger of the syringe supply the pressure to inject 10 ccs of UFL over a period of 30-40 minutes (longer with obstruction of lymphatics). X-rays of the lower limb and trunk are taken immediately after injection to demonstrate the lymphatics and 24 hours later to demonstrate the nodes. This technique outlines the lymphatics along the greater saphenous veins and those of the posterior pelvis, posterior abdomen, posterior mediastinum, supraclavicular regions, axilla and upper limbs. Primary lymphactics of the uterus, other pelvic organs, bowel and lung cannot be demonstrated, but the primary lymphatics of the penis and testis can be shown. In some cases, lymphangiograms are done in conjunction with arteriograms and venograms for better topographical evaluation. This same technique may be applied to the upper limb.

The *interpretation* of lymphangiograms is difficult. Appreciation of their normal appearance is a prerequisite for evaluation of the pathological situation. Normal nodes are rounded or kidney-shaped, having a homogeneous reticular pattern and measuring about one centimeter in diameter.

The indentation at the hilus is more marked if there is fatty infiltration. In contrast, metastatic nodes are normal or enlarged in size and show filling defects in the peripheral part of the node due to the inability of the contrast medium to opacify the metastatic foci. Nodes are not visualized when completely replaced by tumor, but instead displaced lymphatics, collateral channels, or lymph stasis with beading of lymphatics are seen. In malignant lymphomas nodes are regularly or irregularly enlarged and increased in number, having various adenographic patterns. They have been seen by Viamonte et al at different times to have a strand-like net-work, peripheral crescentic opacities due to an uninvolved subcapsular space, and spotted filling defects. Chronic inflammation can mimic metastatic carcinoma, thereby making interpretation less efficient. In this condition there is uniform enlargement of the involved nodes and occasionally irregular filling defects due to the presence of suppuration and fibrosis. It is important to remember that there is no pathognomonic feature for any one condition, and that abnormal morphology and architecture of lymph nodes does not always indicate the presence of a malignant process (1).

Lymphangiography is indicated in the evaluation of the extension of primary or secondary lymph node malignancy; in the differentiation of abdominal masses; in providing information as to the cause of obstructive edema when combined with phlebography; in assisting in evaluation of treatment of malignant disease; and in facilitating pelvic and periaortic lymphadenectomy by staining lymph nodes with a green dye which is injected with the opaque medium (1). Seitzman et al describe the incorporation of I (131) into the contrast medium to treat tumors which metastasize to inguinal or retroperitoneal nodes (for example genitourinary tumours). In addition, this procedure is reputed to be useful for the treatment of malignant lymphomas and subungual melanomas.

Lymphangiography is also used in the study of anatomy and physiology. Herman et al found that the lymphatics filled 24 hours earlier than the nodes, and concluded that the "channels are independent pathways and the nodes are aggregates of lymphoid and reticular tissue built around these channels; they are depots rather than barriers". Wallace et al have shown how lymphangiography can be used to enhance our knowledge of lymphatic dynamics in abnormal states.

Some *complications* of this procedure should be borne in mind. Wound infections, lymphadentis, fever, extravasation of contrast media, swollen extremities, and iodine sensitivity all have been described (2). A more important complication which occurs to some extent in all cases, is pulmonary oil embolism. Radiographically Schaffer et al visualized this complication in 24 of 141 cases. In addition some of these patients had low-grade fever, 3 had mild dyspnea, and 1 had evidence of pulmonary infarction. Theoretically by the use of this technique tumor cells could be dislodged from the thoracic duct and regional nodes, thereby increasing the number of circulating tumour cells and metastasis (2).

In *summary* lymphangiography is a useful procedure, but not without its limitations in application and difficulties in interpretation.

E. P. Braaten, 6T6

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Abstract

Hazards of Endotracheal Anesthesia

Lewis, R. N., Swerdlow, M.: Brit. J. Anes. 36: 504-512, Aug. 1964.

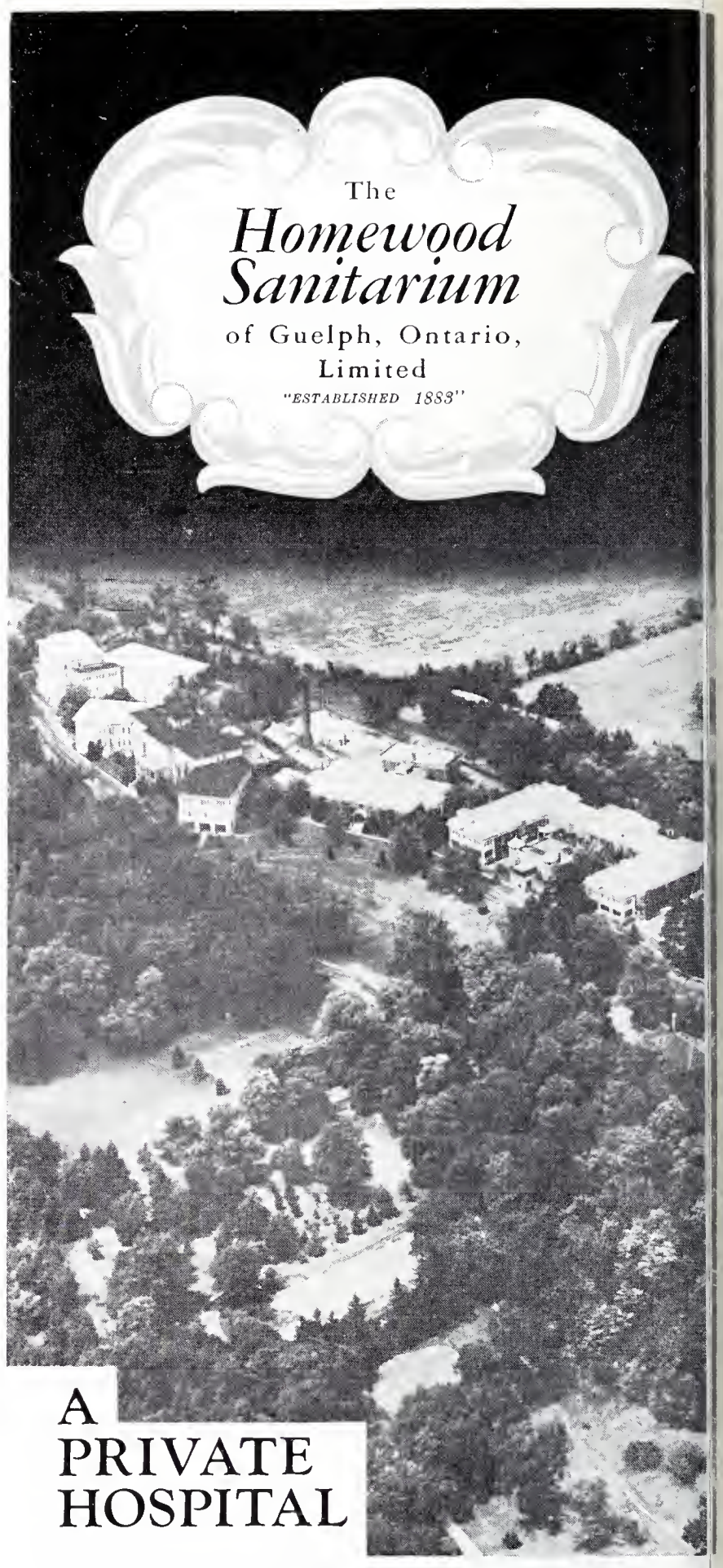
Endotracheal intubation, made a practical procedure since the advent of muscle relaxants, is now widely and enthusiastically used where indicated or if convenient. The authors present a well-organized, extensive and complete review of the literature concerning complications of endotracheal anesthesia and their prevention.

The complications are classified as follows:

1) Complications during intubation
   a) Acute trauma during direct laryngoscopy resulting in bruising, abrasion, stretching or avulsion of tissues.
   b) Acute trauma during insertion of the endotracheal tube which rarely produces serious consequences.
   c) Disturbances of cardiac action ranging from transient changes in heart rate to complete cardiac arrest.
2) Complications during anesthesia — mainly respiraatory obstruction by occlusion of the endotracheal tube or its connections.
3) Complications during extubation arising from aspiration of secretions, inadvertent neglect of throat packs of laryngeal spasm.
4) Complications after extubation — most commonly a post-operative sore throat and rarely laryngitis, edema causing obstruction, membrane formation, intubation granuloma or acute ulceration.

Adequate knowledge, experience and care may prevent many of these complications, but intubation carries a morbidity and mortality rate even in the hands of experts and its use should, therefore, not be indiscriminate.

M.T.



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G. S. BURTON, M.D.C.M., *Medical Superintendent.*

A Precis Of Breast Cancer

B. Zimmerman, 6T5

The study of breast cancer is the study of trends. Since the evaluation of any new technique necessitates collecting cases and survival statistics for periods ranging from five to fifteen years, a decade passes before results are valid. Breast cancer becomes reduced to statistics; a set of figures supports one theory, another disproves the first and a third counters the second.

DIAGNOSIS

One of the main weapons in the fight against this disease is earlier diagnosis. Much of the therapeutics of breast cancer hinges on the fact that the five year survival for patients free of axillary metastases is about 75% and for those with clinically palpable nodes, 30% (26). Two separate articles (1, 2) have noted a recent increase in patients with operable carcinoma, smaller primaries, and less nodal metastases. Also more of them were asymptomatic at the time of diagnosis as compared with past years. McSwain (2) mentions that in the period from 1925 to 1945, 70% of patients had axillary involvement while the period 1956 to 1960 showed only 49.6%. One would expect that the emphasis on earlier diagnosis would be reflected in increasing survival rates or decreasing mortality rates. However, a number of authors (3, 4, 5) call attention to the steady unchanging mortality rates in the United States, Canada and the United Kingdom without any sound evidence that the incidence is increasing. Collins (6) challenges the improving five year survival rate on the basis that the individual cancer patient now still dies at the same time she would have twenty years ago, but today, earlier diagnosis means she will live more years with known carcinoma.

Today, more emphasis is being placed on biological predeterminism; that is, the part that the degree of inherent malignancy of each tumour plays in its prognosis. One pessemistic view (7) holds that only 25% of women will benefit from earlier diagnosis because the fate of the other 75% is predetermined. Biological predeterminism has been calculated in terms of the doubling rate of the tumour. This is based on two premises, one that cancer grows at a regular rate which follows an exponential pattern; the second that the cancer starts as one cell of 10 μ diameter, taking thirty doublings to reach a size of 1.0 cm. The predetermined factor is the speed of doubling times. This has been classified according to slow, medium and fast, but is fixed for each individual tumour. Two studies (6, 8) have calculated fast doubling rates to be under thirty-five days in one study, and seventy-five in the other, while slow is greater than seventy-five and one hundred and fifty days respectively. These calculations are from a small number of cases. Pulmonary metastasis were followed by X-ray in the first instance (6) and mammography in the second (8). It is felt that tumours are being diagnosed late in the doubling scale (twenty to thirty doublings at diagnosis). Since three doublings gives a lump twice its previous diameter and eight times its previous volume, it is easy to understand why a small lump can suddenly seem to enlarge. Collins feels that metastases occur too early for any present method of diagnosis. He calculates that pulmonary metastases occurred fifteen doublings before diagnosis. The other study by Gershon-Cohen showed that slow growing tumours comprised 65% of cases, and these could be benefitted by early diagnosis.

The methods of increasing early detection are:

(1) Self examination.
(2) Periodic routine cancer detection clinics.
(3) Roentgenography.
(4) Thermography.
(5) Cytological examination of nipple secretion.
(6) A high index of clinical suspicion and a generous policy of surgical biopsy.

Shahon (9) reported on 4,956 women, age forty-five and over, who were given annual physical examinations. Thirty-three breast cancers were discovered (1 per every 553 examinations). Fifteen of these women had been performing self breast examination and had missed the lump. The five year survival rates for asymptomatic cases (22) was 100% and for symptomatic (11) was 75%.

Another method that can be used for early diagnosis is roentgenography (10, 11, 12, 13, 14, 15). This can be used for detecting occult lesions by screening or as an adjuvant diagnostic tool for verifying lesions. As a routine screening procedure, mammography is reported to turn up from one to five cancers per thousand women (most report two per thousand). The accuracy of diagnosis as checked by biopsy varies from 80% to 92%, averaging around 85%. Cancer is diagnosed on the basis of an opacity, most often with an irregular nodular outline and fine punctate or broken needle calcifications. Skin thickening (lymphedema), increased vascularity and obliteration of the pectoralis line are other early features.

A newer technique (16) for early diagnosis is thermography, or measurement of infrared radiation emitted by skin. Almost all carcinomas are "hotter" than surrounding breast tissue, while benign lesions are not. This can be measured by an ordinary thermocouple and galvanometer or by exposure of special film. The ther-

mogram is a half tone picture in which hotter areas create lighter grey shades than the normal surroundings. Thus, a malignant lump forms a light grey shadow, which is localized by its position in relation to the nipple (the latter is covered by aluminum foil, a poor emitter, causing a dark black spot).

Cytology (11) has also been used for diagnosis, primarily in cases of nipple discharge. A smear is made and stained by the Papanicolau method. The diagnosis is made from a combination of criteria of malignancy in cells (e.g. atypia, nuclear enlargement, hyperchromatism, clumped chromatin in irregular distribution). The frequency of false negatives reported in one series of 253 patients was 15%, and false positives also 15%.

The last method to be mentioned is still the most important—biopsy. The danger of biopsying a lesion, i.e. cutting blood vessels and lymphatics in the area of malignancy, has largely been relegated to theoretical texts, but the choice of method of biopsying still raises some questions. The aspiration or needle biopsy is a simple procedure, but is subject to a higher degree of interpretive error since the tissue submitted often lacks normal areas of comparison. Sometimes, it consists only of epethelial cells without any ductal or stromal formations. Generally, the excisional (removal of the whole lump) biopsy is the method of choice unless, of course, the primary lesion is too large for this procedure. Although its cuts across microscopic foci of malignant cells, more tissue is submitted to the pathologist. The incisional biopsy, on the other hand, submits only a piece of the tumour and although it is thought by some to entail less manipulation and trauma, (thus decreasing dissemination), it does cut through tumour.

PROGNOSTIC PARAMETERS

This is an area that has filled the literature. Each new method begins by correlating with five year survivals rates, and with one of the older parameters (e.g. axillary nodes).

Some of the older more established prognostic factors are:

(1) Epidemiological—age, menstrual status, pregnancy
(2) Clinical staging
(3) Size of the primary
(4) Axillary node involvement and node levels
(5) Internal mammary node involvement
(6) Morphology of the tumour
(7) Location of the tumour
(8) Delineation of the primary

Some of the newer parameters include:

(1) Nipple histology
(2) Host-tumour response
(3) Steroid hormone excretion
(4) Mammography
(5) Thermography

The older factors are still the backbone of prognosis and probably many of the newer ones will not be used.

Epidemiology: A survey (18) of 1,458 females with proven carcinoma found survivals lower in the young, increasing to the time of menopause and gradually decreasing from forty-five on. (of course intercurrent deaths are higher after forty-five). Treves (19), in a study of 549 female patients under age thirty-five, found 80% were operable and the five year crude survival rate 40.6% which was similar to five year survival for older patients. He did find, however, that prognosis with axillary metastasis was poorer than for older patients. He also found a poor survival for breast cancer and pregnancy—17.9%. Survival with positive axillary node involvement was 20%, the same as non pregnant, but 77% of the pregnant had nodes, compared to 59.1% of the non-pregnant. White (20) found five year survival figures for pregnancy and breast cancer of 13.4%. Later, Bloom (21) reported that the poor prognosis correlated with, and was explained by, a high incidence of these cancers falling into his histological grade III which carries a poor outcome. On the other hand, Bunker and Peters (22) report a survival rate of 47.4% not significantly lower than non-pregnant patients of a similar age. They also found that breast cancer diagnosed during lactation, especially if the patient was actively lactating, carried a poorer prognosis. They feel that the poor prognosis in pregnancy is entirely due to delay in diagnosis. In their series, there was an average delay of two months, part of which was delay in discovering the lump and the rest delay in labelling it malignant. The diagnosis is difficult because the normal physiological enlargement of the breast obscures the lump, or the lump is often misdiagnosed as a lactation abscess. Devitt (23) agrees that Bunker and Peters, and cities seven cases, a high proportion of which were late stage. Five lived five years and three of these are alive at ten years. Most other authors are not as optimistic and feel the tumours grow very fast, due to increased blood supply and estrogen from the placenta with a higher number of hormone dependant primaries than non-pregnant.

Clinical Staging: There are a number of different methods of staging—the Portmann IV Stage; Richardson V Stage; Manchester and Columbia staging, to name a few. A universal method of staging, TNM (tumor, nodes, metastasis), is now being perfected to coordinate all breast cancer statistics. Generally, all stagings are based on:

(1) Size and fixation of the primary
(2) Involvement of axillary nodes clinically, and
(3) Grave local signs, i.e. edema, fixation of the tumour or nodes, ulceration, satellite nodules,, edema of the arm.

Portmann stages I and II are very similar to Columbia A and B, while the later III, IV and C, D are just advanced clinical cancers.

Size of the Primary: This also gives an estimate of prognosis—the larger the primary, the poorer the prognosis. Rigby-Jones (24) gives the following figures for size and five year survival rate:

less than 4 cms — 63%; less than 6 cms — 53%; greater than 6 cms — 36%.

Other studies have shown that the larger the primary, the higher the incidence of axillary node involvement, and similarly, the higher the incidence of internal mammary spread (26).

Axillary Nodes: This is the key prognostic parameter. A refinement of this parameter has been the use of node levels. Berg (27) (1955) described three levels (Level I below pectoralis minor; level II—behind pectoralis minor; level III—above). He found that for carcinoma of a given size, level III gave a prognosis five times worse than that for an axilla free of metastasis. Further, carcinoma less than 2 cms. was likely to metastasize only to levels I and II, but with increasing size, there was increasing involvement of level III. (11% of cases skipped levels). Five year survival figures reported elsewhere were Level I about 65%; Level II, 45%; Level III, 28%) (28).

Involvement of Internal Mammary Nodes: Related to axillary node involvement is the involvement of internal mammary nodes. This is considered a sign of poor prognosis. Internal mammary node involvement varies from 25% (29), found experimentally, to about 30% (30, 31) of cases. It has also been found that about half of the patients with positive axillary nodes had metastasis to the internal mammary chain. Crude five year survival in one study of 250 patients with no nodes, was 84% (10 years — 73%), and with both axilla and internal mammaries — 13% (32). The involvement of internal mammary nodes also varies with the size and site of the primary. Central (subareolar) and medial lesions metastasize more often to the internal mammary chain than lateral lesions. The larger lesions also metatasize here more often. The nodes most often involved are in the second interspace, then the first, third and much less often, the fourth.

Delineation of the Primary: Lane (33) followed 241 patients and found that primaries with irregular contours (¾ of cases) had a ten year survival rate of 38%, but with well circumscribed primaries (¼ of cases), 80% survived ten years. The well delineated also gave a better chance of minimal axillary involvement.

Morphology of the Tumour: Medullary carcinoma with lymphoid stroma have been long known to give a better than average prognosis. Hultborn and Tornberg (34) list:

(a) *Non metatasizing as:*
  (1) Papillary
  (2) Intraductal without stromal invasion

(b) *Rarely metastasizing (always invasive) as:*
  (1) Pure mucinous or colloid
  (2) Medullary with lymphocytic infiltration

Many grading systems have been created on the basis of histology and survival. Hultborn and Tornberg claim well differentiated adenocarcinoma (grade I) rarely metastasizes, whereas grade II (intraductal with stromal involvement) is occasionally metastasizing, and undifferentiated (grade IV) metastasizes widely.

Bloom and Richardson (21) worked out three grades on the basis of (1) degree of tubular formation, (2) regularity of nuclear size, shape and staining, (3) frequency of metotic and hyperchromatic figures. Of 1,409 patients, 26% are grade I (5 year — 75%); 45% are grade II (5 year — 47%); 29% are grade III (5 year — 32%).

Other Criteria for Judging Prognosis

Nipple Histology: Involvement of the nipple (35) microscopically by lymphatic and interstitial spread gave a five year survival of 47%, whereas without nipple involvement, it was 79%. In one study (36), nipple involvement was associated with axillary nodes in 93% of cases, possibly due to peri or retro areolar lymph plexuses.

Host-Tumour Response: Another interesting prognostic feature is the host-tumour response. Berg (36) (1959) found that, in large tumours surviving ten to fifteen years, the primary was either medullary, colloid or anaplastic duct carcinoma with a plasma cellular infiltrate nearly all the way around the tumour. Actuarial survival rates for plasma cells completely marginating the tumour was 73%; incompletely, 58% and absent, 54%. He is not yet sure if this is an auto-immune response or simple chemotaxis.

A second controversial form of host-tumour response is sinus histiocytoses (37) (the extent to which axillary lymph node sinusoids fill with elongated histiocytes). Black and Speer grade the degree of sinusoid filling zero to four, and find a better five year survival for greater degrees. They believe this is an expression of host-tumour response. Berg believes sinus histocytosis in axillary lumph nodes is normal, while another group of investigators (38) could not find any differences in survival with or without histocytosis.

Hormone Environment of Breast Cancer and Prognosis: Bulbrook and Hayward (39) postulate that there are two types of cancer patient; one with abnormal hormonal output and the other with normal. They feel this may be the factor controlling predeterminism. Their series of patients showed some with abnormal urinary excretion of aetiocholanolone and 17-OH corticosteroids. 48% of these were dead in four years. The patients with normal excretion were all still living (series of thirty-eight cases). The tumours of the abnormal excretors grew faster and did not respond to treatment.

Mammography and Thermography: Prognosis as predicted by mammography is simply a classification of the tumour according to one of four radiological types, each of which carries a prognosis. Prognosis by thermography is still in the infancy stages, but it seems that more malignant tumours are "hotter".

TREATMENT

The treatment of breast cancer consists roughly of local and systemic agents.

Local Treatment

The surgical procedures used are: (1) Local resection of the tumour; (2) Halstead radical; (3) Patey modified radical; (4) Supraradicals of Urban and Wangensteen; (5) Simple mastectomy. The choice of procedure varies from hospital to hospital, but there is a trend towards the modified radical which leaves the pectoralis major intact. Urban's supraradical consists of enbloc excision of the internal mammary nodes with the breast, pectoralis major, minor, axillary nodes and about one third of the sternum. The chest wall defect is repaired by a fascia lata graft. Wangensteen includes in the enbloc procedure, removal of the supra-clavicular nodes. The simple mastectomy which does not remove the pectoral muscles is generally followed by extensive high voltage radiotherapy.

Since surgery is a local procedure, it cannot be used indiscriminantely on cases which would better benefit by radiotherapy. Many centres have criteria of operability of varying strictness. In general, the signs of inoperability are: (1) extensive edema of skin over the breast; (2) satellite nodules in the skin of the breast; (3) inflammatory type of cancer; (4) parasternal lymph node involvement; (5) supraclavicular metastasis; (6) edema of the arm; (7) distant metastasis; (8) grave local signs — ulceration, large fixed axillary lymph nodes; (9) advanced age, debility, etc. Haagensen and Stout (40) found that patients falling into the inoperable category had a shorter average mean duration of life after radical mastectomy than those untreated. Better results were obtained by radiotherapy or simple mastectomy. They also developed a triple biopsy technique to further tighten operability criteria. In large tumours, tumours of the inner quadrant or clinical axillary nodes, the internal mammary nodes are biopsied. If the axillary lymph nodes involved are very large, the apex of the axilla is biopsied. In grave cases both biopsies are done. If any of the biopsies are positive the patient is inoperable.

Even the choice of operation has come under fire in recent years. In the last ten to fifteen years, results as good as those for radical techniques have been reported for simple mastectomy and postoperative radiation. Other investigators have shown better results with ultraradical techniques. At present, most articles are calling for a controlled clinical trial of all techniques which will randomize all variables and grade tumours in the same manner.

Some of the papers advocating more conservative treatment are:

(1) Meyer and Smith (1934)—142 cases 8% higher five year simple over radical

(2) Deaton (1955) — 808 cases — 5% higher for simple

(3) McWhirter (1958) —
Simple plus postoperative radiation - 42.9%
Radical plus postoperative radiation - 32.4%

(5) Yale — New Haven Medical Centre — patients 1921 to 1957—no difference

(6) Kaae and Johansen (41) (1963-4) — 187 patients given McWhirter technique — 166 given ultraradical
Crude five year survival — Simple, 67% — Ultra, 69%

(7) Devitt (42) (1963) — 227 conservative surgery; 534 radical — almost identical survivals

(8) Crile (43) (1964) — 69 Simple, 62 Radical
Crude five year survival —
Simple, 64% (84% stage I)
Radical 58% (61% stage I)

Yet other investigators have been unable to duplicate these results. Urban (44), who performs the ultraradical mastectomy, shows five year survival figures (265 patients) of 68%, and of these 32.5% had involved internal mammary nodes (54% with positive nodes overall). The survival for all patients with positive internal mammary nodes is 46.5% (clinically free of disease at five years, 40%). These patients would of course be ruled inoperable by the criteria of Haagensen and Stout. Still, it is probably the feeling of many centres that spread to internal mammary or supraclavicular nodes is not amenable to surgery, due to the anatomical relations. Many feel the ultraradical is useless mutilation and harmful by further dissemination of disease and slightly higher operative mortality. At the other extreme, Porritt (45) (1964) mentions the possibility that lymph nodes are "brakes" on the disease and does only a local segmental oval excision of the growth via a submammary or paramammary approach. He makes no attempt to clear the axilla. In 263 cases randomly selected for local or radical, the five and ten year survival results for local were 65 and 34%, while for radical, were 45 and 34%.

The middle of the road approach is now the modified radical (Patey) which preserves the pectoralis major. Handley, in performing this operation, does a routine internal mammary node biopsy and if he finds it positive, uses a simple mastectomy and postoperative irradiation instead. The advantages of the modified radical mastectomy are: (1) cosmetic, (2) stronger arm, (3) less lymphedema. Halstead enthusiasts maintain the axilla cannot be properly cleared without first removing the pectoralis major.

As mentioned before, there has not been a controlled evaluation and comparisons of the figures quoted should not be made too freely.

One important factor which has not been controlled in these studies was the use of irradiation. Here again, the choice of methods is under fire. Irradiation is used both as a local method of cure and as palliative treatment in hopeless cases. It is felt that lymph node metastases can be controlled by vigorous irradiation, but the frequency of control and the permanency is uncertain.

General Indications for Irradiation

(a) *Preoperative*—Ash, Peters and Delarue recommend preoperative irradiation in the late stage cancers. Other centres believe this needs further evaluation.

(b) *Postoperative irradiation*

(1) Not used in outer quadrant lesions without microscopically verified metastasis to the axilla.

(2) With positive axillary nodes microscopically post-operative irradiation is used routinely including the internal mammary and paraclavicular nodes.

(3) If the primary lesion is central or medial in location, postoperative radiation is used more liberally, even with no demonstration of positive axillary nodes.

(4) When the primary is thought to have been incompletely resected, more extensive chest wall irradiation is used.

(5) Inoperable carcinoma is treated by vigorous irradiation to the chest wall, breast and lymph node areas.

(6) If local chest wall recurrence develops and the patient has not received previous post operative irradiation, they may be given treatment to the chest wall and regional nodes. In a recent clinical trial (46), it was found that patients treated prophylactically postoperatively with irradiation had no difference in crude survival rate compared with another group given irradiation only after a recurrence or metastasis to nodes developed. (Selection for grouping was made on the basis of day of birth — even or odd).

Another recent randomized survey (47) presented five year survival results for radical mastectomy alone and radical mastectomy plus postoperative radiation with ortho-voltage equipment. (Irradiated internal mammary and supraclavicular nodes). The five year survival results with radiation were 50% (8 year — 35%) and without radiation five year was 52% (8 year — 41%). They concluded that postoperative radiation after radical mastectomy was not justified using ortho-voltage. They conceded that another investigator using 2 MeV equipment may have given better results.

Radiotherapy is also valuable as a palliative measure for local skin and subcutaneous recurrences as well as distant osseus metastasis. This can be accomplished by any one of a number of methods; i.e. (1) external applicator (mold), (2) radium implants, (3) ortho-voltage irradiation, (4) superficial X radiation (low KVs).

Radiation used for relief of bone pain gives relief of symptoms in 50% of cases. Osteolytic lesions are more responsive than osteoblastic. Liver metastasis are not radiosensitive. Esophageal obstruction and superior vena caval compression syndrome due to lymph nodes can be treated by radiotherapy. Ovarian irradiation can be used if surgical oophorectomy is contra-indicated.

Medical Management

The systemic treatment of breast cancer involves hormones and chemotherapy. Hormonal treatment can be ablative or additive using steroids, estrogen and androgen. It is generally conceded that hormonal management, although not curative, is at the very least palliative. A plan of management might resemble the following:

Females *with* estrogen secretion as judged by:

(1) Menses (considering recently postmenopausal women as still having slight estrogen secretion)

(2) Karyopyknotic index greater than 10% (refers to nuclei in vaginal scrapings)

(3) Cornification of the vaginal cytoplasm,

can be treated by oophorectomy, either surgical or radiation, and if they get a good response, one can consider treatment by hypophysectomy, adrenalectomy or prednisone (all three are based on the principle of decreasing adrenal secretion of estrogen).

If these patients then become refractory, they are placed on the regimen of treatment used in the first place for women who did not show estrogen output. They are given estrogens or possibly androgens, prednisone and then chemotherapeutic agents.

The controversy in hormonal therapy revolves around:

(1) Prophylactic versus therapeutic castration
(2) Hypophysectomy or adrenalectomy or both
(3) The value of androgens
(4) The value of chemotherapy
(5) The evaluation of different derivative agents purporting longer durations of remissions or fewer side effects.
(6) When to progress from one step to the next.

In general, results of medical management are discussed in terms of objective and subjective regressions rather than survival rates. For the purpose of evalu-

ation, only objective regressions are considered, while subjective are mentioned in passing.

Criteria for regression:

(1) Measureable tumour decrease clinically or radiologically in the primary site or one or more dominant metastatic lesions without progression of the other metastasis and no new metastasis for six months.

(2) Recalcification of osteolytic lesions.

The problem of when to castrate the premenopausal female has been controversial for many years now. Most centres do not advocate prophylactic castration because it does not cure and does eliminate a guide for later endocrine treatment, to say nothing of the emotional and physical effect. Two series (48, 49) recently reported findings on the subject. One found that prophylactic castration offers no difference in survival rates as compared to therapeutic castration. The other found that X-ray castration gave slightly better results than treatment without castration. Most centres recommend surgical castration if possible. The hormone level drops more abruptly, and there are fewer failures. The radiotherapy failures may be due to poor technique or the ovaries may be in an abnormal anatomic position.

There are similar differences in opinion about the superiority of either hypophysectomy or adrenalectomy. Some investigators feel better results are obtained by hypophysectomy, especially in patients who have responded well to oophorectomy. Others claim that complete hypophysectomy is often not accomplished, and that the management of these patients postoperatively is difficult. Most feel that there is nothing to be gained by both procedures being done. MacDonald (50) found no significant difference between the two procedures.

Chemotherapy is still in most cases, a late stage palliative procedure. The agents used have been cyclophosphomide, thiotepa, vincristine and vinblastine. Reports have also been published on the use of nitrogen mustard derivitives preoperatively, and postoperatively. As well, the wound and tumour site is washed with nitrogen mustard during the operation, and postoperatively for some days. The results have been inconclusive.

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Dr. Ignaz Philipp Semmelweis, an Hungarian Obstetrician in the nineteenth century, laid the foundation of modern aseptic technique. It was his discovery of the cause of childbed fever, *puerperal sepsis*, its mode of infection, the mechanism of its transmission and the prevention of this disease that revolutionized medical technique.

Ignaz Semmelweis was born in Ofen, Hungary on the 1st of July, 1818. He was the son of a poor peasant grocer. His primary education was detailed enough to allow his entrance to the field of law at the Vienna University. During that time, Hungary was part of the great Austrian Empire. In contrast to the high social, political and educational stature of Austria itself, Hungary was quite backward and poor due to excessive taxation by the Austria Emperor. Indeed, an Hungarian was viewed with scornful, mocking eyes. Because of these prevalent ideas, Ignaz was to endure near poverty subsistence, poor clothing and food, and most important the stigma of being an Hungarian during his stay in Vienna.

Unable to tolerate the course in law, Semmelweis began the study of medicine at the University of Vienna. He was impulsive, enthusiastic, ill-bred, and lacked social grace. He engaged in his studies with such vigor that he outraged his professors by not accepting without question, theories formulated on inexplicable hypothesis. He constantly interrupted classes to challenge or demand explanations of unscientific ideas or theories. His flood of questions so infuriated his teachers that he soon became the object of their scorn, insults and venom. Not being able to understand the reason for this hatred, a bewildered Ignaz left Vienna University to complete his education at the medical school in Hungary.

However, finding the course extremely inadequate, he returned to Vienna in 1840 to begin the remaining three years of his undergraduate study. With such extraordinary enthusiasm did he study Medicine, his thirst was noticed by a few enlightened, liberal professors. These men guided, supported, and encouraged Semmelweis to the degree that without their trust, his great discovery would not have been possible.

On graduation, Ignaz Semmelweis turned his attention to obstetrics. Soon he became 1st assistant in the first Division of the Lying-In branch of the Vienna General. The Lying-In-Division of the Vienna General was divided into three divisions. The First, the public patient ward, was under the directorship of Dr. Klein. This doctor obtained his post by political manipulation and consequently, spent most of his career in preservation and justification of his position. He was an administrator who did not want attention, progress or deterioration. He was fanatically loyal to his superiors and intensely hated men of brilliance or originality. He was intolerant of any change; changes in theories of causation, treatment, or prevention of diseases. He represented the majority of doctors in the Vienna General who received staff positions by political manoeuvring instead of medical brilliance. These were the men against whom Dr. Semmelweis had to defend his theories of causation and prevention of puerperal sepsis.

Puerperal sepsis, itself, was the scourge of all Lying in Hospitals in Europe and America. The disease inflicted mortality rates of up to 35% to both mother and child in Vienna. In Paris at the Hôtel Dieu the maternal mortality rate was 50%. There were four years at the University of Jera when not a mother left the hospital alive. Indeed the death bell never ceased!

Semmelweis was appalled at the incidence of childbed fever. He devoted his spare time doing dissections on women who had died of puerperal sepsis and he tried in desperation to find from his anatomical studies, the cause. One day, by accident, the professor of pathology nicked himself with a knife during an autopsy and shortly died of cadaveric poisoning which presented with all signs, symptoms, and pathological features of puerperal fever *but* in a male. Semmelweis deduced that there was more than coincidental relationship between the two disease phenomenon. Cadaveric material on the hands of instructors and students (men fresh from autopsy who but wiped their hands on their lab coat) was introduced into the vaginal canal during the course of vaginal examination. Thus logically, to stop this pelvic contamination, one had to wash ones hands. However, never has such a simple deduction and solution been met with such opposition.

Doctors and students scoffed at the simple solution. Midwifes and attendants protested their loss of dignity by washing their hands. The women patients themselves thought this ill-bred Hungarian washed his hands because their vulvar regions were unclean. The great Obstetricians of Europe, Scanzoni, Mauriceau and even the famous Simpson viewed the discovery with scorn even in the light of overwhelming proof in support of his theory.

Semmelweis ordered, as 1st assistant, that before any pelvic examination the hands had to be washed meticulously. Miraculously, the incidence of childbed fever reached as low as 1.5% per annum of all obstetrical admittance. In light of this evidence, he met unwavering opposition. Dr. Klein, hating change and Semmelweis's brilliance, would not renew his position of 1st assis-

tant. The great Europian Obstetricians labelled him the "Pesth Fool." Medical directors of the Vienna General would not grant him a staff position. Finally he was forced to take refuge in his homeland, Hungary.

Soon after his appointment to the staff of the Budapest Hospital, Semmelweis was made head professor of obstetrics. In contrast to the Vienna General, the hospital had a small cramped obstetric ward with a maximum capacity of some 300 patients a year. As professor, he enforced the strictest procedure of cleanliness in the management of obstetrical patients. As in Vienna, the mortality rate of puerperal fever diminished drastically such that in 1 year not one admitted case, died of the fever. A truly remarkable feat! Still all over Europe and America, the mortality rate averaged between 30-40% — a useless wastage of human life in the light of his discovery.

He wrote articles to obstetrical journals, letters to head obstetrical professors all over Europe, a book with supporting statistical data and experimental results about childbed fever. He was met with the same strong opposition from all flanks. Indeed he was the "Pesth fool."

At the end, Semmelweis became a driven man. He became more agitated and would display a violent temper at the least mention of his theory. His uncontrollable temper and outbursts finally lost him the right to treat any gynecological problems at the Budapest Hospital. He unfortunately bordered on the verge of insanity. At this time he went to a printer and had printed circulars which stated "Young men and women. You are in marked danger. The peril of childbed fever menaces your life! Beware of doctors, for they will kill you" (1). He ran through the streets of Pesth distributing the handbill to any man, woman or child. He smiled. His duty to mankind had been fulfilled.

In the end, he was admitted to an asylum in Vienna. He spent his dying days in a dark chamber under lock and key, delerious with the fever of cadaveric poisoning, the same disease to which he devoted his life to eradicate.

A. G. Logan, 6T6

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Tumours of the Urinary Bladder

R. Price 6T5

ETIOLOGY

It was in 1895 that Rehn, in Germany, noted that 3 out of 45 men working in a fuchsin factory in his area, had developed tumours of the urinary bladder. Upon more closely examining this unusually high incidence, he attributed the tumours to the aniline which was being used in the manufacture of the dyes. He suggested that this was carcinogenic to the urinary bladder. He postulated that the aniline gained entrance to the body by inhalation, skin contact, open wounds and even accidental ingestion. It was then excreted in the urine and once in the bladder it exerted its carcinogenic effect. Over the years many other cases of occupational bladder cancer associated with the manufacture of aromatic amines have come to light. It has since been shown that the carcinogenic agent is not aniline itself but other aniline derivatives such as 2-naphthylamine, benzidine and 4-aminobiphenyl. The idea of a urine-borne carcinogen is supported by the fact that the majority of malignant bladder tumours occur in areas most exposed to the urine, such as the trigone and ureteral orifices and dependant parts of the bladder. Similarly, if one considers the frequent association between renal pelvic tumours and the histologically identical tumours of the urinary bladder as multiple primaries, rather than due to *seeding* of tumour cells, then this too would suggest a urine-borne carcinogen.

On testing the carcinogenicity of a number of aromatic amines in the rat's bladder, it was demonstrated that a number of the ortho-amino phenols were carcinogenic.

It has long been recognized that spontaneously arising bladder tumours are identical histologically and clinically with the occupational or aniline-tumours. Thus, one is tempted to consider carefully any endogenous ortho-amino phenols as possible etiologic agents in spontaneous bladder tumours. Consequently, much attention has recently been focused on tryptophan and its metabolism as a possible source for endogenous carcinogens. At least three of the intermediary metabolites of tryptophan, i.e., 3-hydroxy-anthranilic acid, 3 hydroxy-kynurenine and 2 amino-hydroxy-acetophenone are ortho-amino phenols and these have recently been shown to be carcinogenic on administration to mouse bladders. The total amounts of these intermediates to be found in an individual's urine vary greatly, and the amounts of the substances which are present in the presumably inert conjugated form as sulphates and glucuronides is not known for certain. However, about 50% of patients with bladder tumours have been shown to have high concentrations of these carcinogenic intermediates. At present, this investigation of tryptophan intermediates as carcinogens is a rather hopeful area in the ultimate solution to bladder cancer and indeed perhaps other cancers as well.

INCIDENCE

Bladder tumours are the most frequently encountered malignancies of the genito-urinary tract. They are over twice as common in males as females. They are more common in urban areas. The overall incidence is very low until the third or fourth decades after which it rises. In the population over 40 years of age, it has an incidence of approximately 17 per 100,000, and in the over 70 age group this incidence has increased to about 130 per 100,000. The incidence of bladder tumours is increasing and has doubled in the last 20 years.

PATHOLOGY

Over 95% of the bladder growths encountered have arisen from the transitional epithelium. Approximately 25% of the tumours are multiple. These tumours may or may not infiltrate the bladder wall.

Consider first the non-infiltrating type of tumours. This implies an intact basement membrane. Transitional cell carcinoma, Grade I, is a villous growth which sprouts from the mucosa. It consists of a central stalk, or pedicle, of connective tissue and blood vessels from the submucosa, which is ensheathed by a basement membrane. Surrounding the basement membrane is a "coat" of what appears to be normal transitional epithelium. It may be a single villous process but more often it is a cluster of villi attached to the bladder wall by a narrow stalk. It is important to note that although it is apparently normal transitional epithelium covering these villi, they are considered by most as potentially malignant and handled accordingly.

Transitional cell carcinoma, Grade II is a papillary tumour, as above, but having obviously malignant cells making up its mucosa. A number of the villi may be fused together in varying degrees resulting in tumours which vary in appearance from a feathery surface to a solid surface.

The infiltrating tumours are those in which malignant cells have penetrated the basement membrane and hence are present either in the stroma of the pedicle or in the bladder wall.

Transitional cell carcinoma, Grade III is such an infiltrating tumour. Consisting of malignant transitional cells of varying degrees of differentiation, the short thick papillary growths are usually fused giving the whole tumour a rather solid appearance. The surrounding bladder mucosa may be edematous and irregular. When the stalk becomes invaded by a sufficient number of tumour cells to embarass the blood supply to the intracavitary portion of the tumour, then erosion and ulceration result in hemorrhage of varying degrees. Thus, as the tumour cells infiltrate more and more deeply, the intracavitary, papillary structure may degenerate and become detached, resulting in a rather solid infiltrating mass of malignant transitional epithelial cells. The appearance of such a "solid" component is a poor prognostic sign. These cells may be either easily or with difficulty identified as having arisen from bladder mucosa, i.e., well or poorly differentiated. As with most other tumours, the well differentiated are the least malignant while the anaplastic varieties are the most malignant. However, as shall be seen later, the cell-type or histological grade of the tumour is not the most important variable with respect to prognosis.

Squamous cell carcinoma is seen fairly frequently, and it is probably a results of metaplasia from transitional cells. Grossly, such tumours are often flat, nodular, ulcerating, non-pedunculated masses which project intravesically only very slightly. Microscopically it is typical squamous cell carcinoma.

Adenocarcinoma of the bladder is rather uncommon, and when it is found it is usually considered to have arisen via metaplasia or from cystitis glandularis or perhaps from urachal remnants. They are usually sessile, ulcerated and deeply infiltrating carcinomas.

Non-epithelial tumours are extremely rare, making up less than 1% of new growths of the bladder.

PROGNOSIS

In considering the prognosis of bladder tumours, naturally the infiltrating variety are the ones to be dealt with, for, until the tumour infiltrates it is potentially 100% curable.

As noted above, among the infiltrating tumours, the well-differentiated ones are the least malignant and the undifferentiated or anaplastic types are the most malignant. Presumably this means that the less the differentiation the faster the penetration of the bladder wall. It has also been stated above that the histological grade is not the most important factor in establishing a prognosis, though granted, it has considerable bearing. However, the incidence of metastases and extravesical spread, whcih are indicative of inoperability, varies directly with the depth of tumour infiltration. The lymphatics of the bladder wall are concentrated mainly in the outer one-half of the muscular layer. Hence the half-way level within the muscularis is the approximate point in the course of infiltration at which curability abruptly diminshes. Knowledge of the prognostic importance of the depth of infiltration has lead to the practice of clinically estimating the depth of tumour infiltration (i.e., staging). This is done preoperatively on the basis of data gained from cystoscopy, bimanual examination, and biopsy.

The stage of a tumour, as determined by its depth of penetration, is outlined below, along with the approximate 5 years survivals.

Stage	*Depth of Infiltration*	*5 Yr. Survival (Treated)*
O	Mucosal (non-infiltrating)	Theoretically 100% curable
A	Submucosal	80%
B1	Muscle (invasion less than ½ way)	60 - 70%
B2	Muscle (invasion greater than ½ way)	15 - 20%
C	Perivesical tissue	less than 10%
D (optional)	Known metastases	less than 3%

Thus, in attempting to arrive at a prognosis in a given case, one must utilize all of the information available which includes both clinical stage and histological grade.

SYMPTOMATOLOGY

Recurrent, painless, total hematuria is most often an indication of a bladder tumour. It is the mode of presentation in about 75% of the cases. Thus, any degree of hematuria warrants a thorough investigation. Most of the rest present with indications of bladder irritability such as frequency, urgency or pain. Some feel that bladder irritability indicates infiltration but this isn't invariably so. A few patients without symptoms may be found on investigating occult blood or cystitis. And, very occasionally, in long-undetected cases the tumour may present as urethro-vesical obstruction, pain in the bladder, rectum, pelvis, flank, back or leg, oedema of the leg from venous obstruction or even uraemia.

DIAGNOSIS

Bladder tumour should be a primary consideration in a patient over 40 years old presenting with hematuria, either gross or microscopic, particularly in the absence of radiological abnormalities of the upper G-U tract, when TB cultures are negative and with a normal prostate. However, bladder tumours can co-exist with other genito-urinary lesions.

In industries in which the employees handle carcinogenic compounds, routine periodic examinations, with emphasis on the genito-urinary tract, are the rule and often result in an early diagnosis.

Exfoliative Cytology: This relies on the examination of stained smears of urine which may contain desquamated cells. After trial for a number of years this technique has not proved as promising as was first thought. It is felt that it is only of value with the highly malignant infiltrating tumours and is relatively useless in recognizing papillary non-infilrating tumours, the stage at which they must be recognized for cure.

Lactic Dehydrogenase: Many patients with carcinoma of the bladder or kidneys have an increased lactic dehydrogenase activity in their urine. But, other conditions such as urinary infections and myocarditis can lead to false positive results and so this relatively non-specific elevation cannot be used diagnostically.

Cystoscopy: This is probably the commonest and most useful means of diagnosing a bladder tumour. It is generally performed under a local anaesthetic, however, a general anaesthetic may be required for the more apprehensive patient. Either way, a thorough inspection of the bladder surface is imperative. If any tumour, or tumours are discovered the exact number, size, location and growth margins must be noted.

Rectal Examination: If the palpating finger can feel the mass in the bladder wall, above the prostate, then it is probably a deeply infilrating tumour.

Urography: Radiological contrast techniques such as an IVP are required to demonstrate whether or not there is co-existence of a renal pelvic tumour. Ureteral obstruction due to tumour involvement of the vesico-ureteral junction may be demonstrated. Also, the cystogram may show a filling defect with a papillary tumor, or perhaps flattening of the bladder wall in the area of an infiltrating growth.

The following investigations must be conducted under a general anaesthetic:

1) *Bimanual Examination:* This technique requires an empty bladder and a relaxed patient in the lithotomy position. With the first two fingers of one hand palpating per rectum and the other hand suprapubically, a careful palpation of nearly the entire bladder and its inferolateral ligaments is possible. In all cases, gentleness is mandatory to prevent bleeding. This technique quickly demonstrates the lack or presence of extravesical spread and thus may indicate inoperability of a specific tumour. Generally if a tumour can be palpated this is a poor prognostic sign, for it usually indicates invasion greater than one-half way through the muscularis. However, this is not invariably so and some pedunculated tumours confined to the mucosa may be vaguely palpable. As well as palpability of the tumour, its degree of mobility must be assessed. An immobile fixed mass is of serious prognostic significance. Conversely, impalpable tumours have probably invaded less than half-way through the muscularis and are treatable transurethrally. There are three common sources of error involved in the interpretation of palpable induration in the bladder. The first of these is a mass within the bladder, such as a stone. Secondly, inflammatory induration of the bladder wall as after irradiation may lead to error, and thirdly, an extravesical mass closely associated with the bladder such as a colonic diverticulum.

2) *Biopsy:* This technique may be helpful with a doubtful diagnosis such as with a flat tumour. Also, it may add much valuable information concerning the depth of infiltration and degree of cellular differentiation when the diagnosis is obvious. It is performed transurethrally with a resectoscope.

These various techniques to establish a clinical stage and a histological grade for the tumour are of the utmost preoperative importance. As stated by Campbell "A complete preoperative classification of an infiltrating tumour is necessary if treatment is to be selected on a reasonably sound basis and if the efficiency of the method that is used is to be compared later with that of a different procedure for another tumour of the same or practically the same degree of potential curability."

COMPLICATIONS

Bladder tumours may produce a variety of complications. The usual complications of malignancies such as direct extension and metastases are, of course, encountered here. Direct extension may, for example, result in vesico-rectal fistulae or vesico-vaginal fistulae. These tumours usually metastasize to the regional lymph nodes, skeleton, lungs and liver in that order of frequency. They may also disseminate widely and result in generalized carcinomatosis. Necrosis and ulceration of the tumour surface may result in a cystitis characterized by irritable bladder. Persistant small hemorrhage may lead to an iron deficiency anemia while massive hemorrhage may result in bladder distension. Tumours near the ureteral orifice may lead to obstructive uropathy, and indeed, if both ureters are involved, uraemia may eventually supervene.

TREATMENT

The most important factor blocking the road to cure, as it were, is a delay in diagnosis. This, of course, is unavoidable when symptoms occur late. However, it is unforgivable when symptoms are ignored. As noted previously, and it certainly bears repetition, any degree of hematuria warrants a full investigation.

There is wide variation in the curability of bladder tumours. This, along with the fact that the results of different methods of treatment are not really comparable unless the tumours are comparable, has lead to many

exponents of many methods of bladder tumour treatment. The most important factor in determining treatment has already been stated—the clinical staging of infiltration. Other factors are the histological grade of malignancy, tumour location, size, number, localization and the rate of recurrence.

Most papillary tumours are easily destroyed by transurethral resection and fulgurization. Because bladder tumour cells have an inherent ability to "seed" on normal bladder mucosa, distilled water rather than an isotonic solution, is used to irrigate the bladder when carrying out such a procedure. After treatment of any bladder tumour by transurethral methods, follow-up cystoscopies must be carried out at regular intervals, for recurrences are often seen. Cystoscopies should be repeated every 3 months for the first two years, every 6 months for the next 2 years, and then once a year for the next 5 years. Of course, any recurrences discovered during these cystoscopies would be dealt with as indicated and the interval between cystoscopies altered accordingly.

Multiple papillary tumours of the bladder present a rather difficult problem in management. Most of the tumours are of a low-grade malignancy and are non-infiltrating. If possible, the tumours are best removed transurethrally and then the bladder mucosa subjected to careful follow-up cystoscopies. It is in this treatment of multiple papillomatosis that chemotherapy has had it greatest success against bladder tumours. Although many agents have been tried over the years, Thiotepa would seem the best. Thiotepa is a polyfunctional alkylating agent with a radiomimetic action. For topical administration, it is generally instilled into the bladder by a catheter. The "safe-effective" dose would appear to be 60 mg. in 30-60 cc. of distilled water. This is retained in the bladder for two hours. An alternative method of administration would be, using endoscopic means, to inject at each tumour site about 5 cc. of a 2 mg/cc normal saline mixture. A course of such therapy consists of this treatment once a week for 4 weeks. Repeat courses are permitted if indicated. The great danger in using this drug is a severe and possibly even fatal bone-marrow depression. Consequently, the WBC and platelet count should be closely followed, stopping treatment when the WBC is less than 3000. It seems that direct injections into the tumour site have the more depressant effect on bone marrow and so the topical instillations are currently more popular. Thiotepa appears to poteniate tumour response to radiotherapy and use has been made of this. However, they have an additive depressant effect on bone marrow. Intracavity irradiation has also been used in the treatment of multiple papillary tumours. Radioactive colloidal gold instillations have proven effective for superficial malignant tumours. However, recurrences are more difficult to manage, and further irradiation may lead to vesical contracture. Consequently, this method has been largely abandoned. In severe cases of multiple papillary tumours, in which, using one or more of the above methods of treatment the recurrences are too fast and too many, then as a last resort a total cystectomy would have to be carried out. This would have to be accompanied by one of the forms of urinary diversion available. These are considered below in relation to simple cystectomy.

Infiltrating tumours vary widely in their nature and behaviour. Methods of treatment range from the very conservative to the very radical. The more important of these methods are considered below.

Fulgurization is inadequate for infiltrating tumours becauses the heat doesn't penetrate deeply enough. Transurethral electro-excision is most suited to tumours occupying the trigone and bladder base. It is a two-step method, the first step consisting of resection of the intravesically projecting tumour. Secondly the bladder wall is resected as deeply as seems necessary. Haemostasis is accomplished by fulgurization. This method is particularly suited to elderly patients who would be unable to stand a more major procedure. It seems to give great relief of pain and vesical irritability. Conceivably, by this method, tumours which have invaded less than halfway through the muscularis are curable if completely resected. However, the uncertainty of complete resection by such a closed procedure is a definite disadvantage of this method.

Radiation of bladder tumours may be accomplished with external, intravesical or interstitial sources. Using an external source such as the Cobalt Bomb, the whole bladder is irradiated. The maximum dose usually recommended is 6000 R given as 200 R/day for 5 days a week for 6 weeks. Many tumours of the bladder are relatively radio-resistant and apparently the lethal dose for the tumor is dangerously close to the lethal dose for healthy tissue. Furthermore, previous irradiation is a contraindication because the patient's tissues do not tolerate overdosage. Intracavity irradiation, perhaps employing a radium capsule within the lumen of a Foley catheter is useful in poor risk patients with small superficially infiltrating tumours that are widely scattered. Interastitial irradiation, accomplished by implanting Radon seeds into the tumour, either transurethrally or by open operation is best used with localized superficially infiltrating tumours.

Beyond these above methods of treatment, the surgeon may resort to various degrees of removal of the bladder, with or without neighbouring structures. Segmental resection, which means the removal of a piece of the bladder wall (total thickness) with an adequate margin around the tumour tissue is currently obscured by more radical surgery which is attempting to improve the prognosis with bladder cancer. However, it is an effective method of curing many patients with tumours infiltrating less than half-way through the muscularis. The surgeon must be extremely careful, when performing an open operation on the maligant bladder, to avoid implantation of tumour cells in the wound. This oper-

ation becomes a more difficult procedure when the tumour involves the trigone or bladder neck area but this isn't a contraindication in the male patient. However, in the female patient, resection in this area may result in incontinence. This operation is contraindicated when too large an area must be resected, for this would result in a bladder of very limited capacity. Similarly, widely separated tumours would mean resection of too much bladder tissue. A poorly delineated growth would make it impossible to obtain an accurate margin. Of course a patient who is a poor surgical risk or a patient with a deeply infiltrating tumour which is no longer localized to the bladder would not be a candidate for this operation.

Simple cystectomy consists of removal of the entire bladder, prostate and seminal vesicles, without a node dissection and leaving the remaining pelvic structures intact. Naturally, such an operation must be preceded or accompanied by surgical diversion of the urinary stream above the bladder. A number of such diversions are available, all having certain undesirable facets.

They are:

(1) Uretero-sigmoidostomy, which is complicated by hyperchloremic acidosis and renal infection.

(2) Rectal bladder which necessitates a life-long colostomy.

(3) Ileal conduits which are associated with stomal and collecting troubles.

(4) Enteroneocystoplasties, very radical surgery which may be followed by nocturnal incontinence, and

(5) Others, such as Nephrostomy and Ureterostomy which would probably only be used for palliative purposes.

Simple Cystectomy would currently seem best suited to bladders in which the tumour does not suit segment-resection for one of the above mentioned reasons. Since it is a major surgery, it should be performed in expectation of a cure and so only when the tumour is confined to the bladder wall, preferably less than one-half way. Radical cystectomy, a simple cystectomy plus complete node dissection is an almost impossible operation. There is also evidence for a fairly high incidence of hematogenous spread of the bladder tumour thus negating much of the value of node dissection. The most radical surgery as yet performed for bladder cancer is probably the now abandoned pelvic exenteration which consisted in bilateral cutaneous ureterostomy, colostomy and removal of the bladder and all pelvic organs, including rectum, pelvic peritoneum and retroperitoneal lymph nodes. Indeed, the multiplicity of treatment methods now available for bladder tumour, implies that no one method yet devised is wholly successful, or is in fact, even satisfactory.

ACKNOWLEDGEMENT

I wish to thank Dr. W. K. Kerr for the opportunity afforded me this summer to work in the Division of Urology of the Department of Surgery where my interest in "things" urological" was greatly stimulated.

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Abstract

Abnormal Blood Coagulation in Carriers of Hemophilia

Miller, S. P., Siggerud, J.: J. Lab. Clin. Med. 63: 621-637, Apr. 1964.

An investigation was performed of coagulation factors in 30 women with at least one hemophiliac son. Results were compared with 30 normal women of similar age. Bleeding time, coagulation time, prothrombin time, partial thromboplastin time and the tourniquet test showed no difference between carriers and normals. But the A.H.G. level in carriers was 75% of the mean normal value. On the basis of these results, a probability curve was constructed which, using the individual's A.H.G. level, may predict her chances of being a hemophilia carrier.

Consumption of proaccelerin and prothrombin was delayed in carriers and this finding may confirm the diagnosis of the carrier state in borderline cases.

M.T.

On Inspection - Answers

1. This skull X-ray of a child with Letterer-Siwe disease —a form of the *reticulo-endothelioses,* demonstrates the characteristic "punched out" lesion.

Classification:

A. Primary Cellular Proliferation (Histiocytic Granulomatosis)
   1. Eosinophilic granuloma
   2. Hand-Schüller-Christian disease
   3. Letterer-Siwe disease

B. Secondary Cellular Proliferation (Lipid Storage Defect)
   1. Niemann-Picks
      (a) adult form
      (b) infantile form
   2. Gaucher's disease
      (a) adult form
      (b) infantile form

Most probably the histocytic granulomatoses are all different manifestations of the same process, and only vary in degree. Eosinophilic granuloma involves mainly bone, occurs at an older age, and has a better prognosis. Hand-Schüller-Christian disease tends to occur at a younger age, be mainly of bone, and be more chronically progressive with a guarded prognosis. Letterer-Siwe disease presents a pattern of deeper visceral involvement in addition to bone, is rapidly fatal and occurs in the young child. It is often accompanied by pleomorphic skin rashes, lymphadenopathy, hepatosplenomegaly and cachexia.

The malignancy of these conditions has been questioned and probably lies intermediately between benign and malignant.

2. This is an example of *bilateral nephroblastoma* (Wilm's tumor). This tumor constitutes approximately 10% of tumors in children. Males and females tend to be equally effected. The average age of onset is 3 years; however, the tumor has been reported to have occurred *in utero* and in adults.

Clinically the most common presentation is a mass (50%), followed by pain, malaise, haematuria (6%) and polyuria.

It is important to differentiate Wilm's tumor from neuroblastoma:

Nephroblastoma	*Neuroblastoma*
History:	
As above	40% may present with bony secondary
Physical:	
Usually smooth, firm abdominal mass, lying toward the flank	Often lobulated, immobile firm abdominal mass extending across the midline
Occasionally hypertension	
Urinalysis:	
Microscopic may show red blood cells	Negative
X-ray:	
A mass, often with concentric rings of calcification	A mass with flecks of calcium
IVP:	
Evidence of distortion and displacement of renal pelvis. The tumor mass may concentrate and excrete a small amount of dye.	Reveals downward or lateral displacement of kidney with little alteration in pelvic architecture.
Metastases:	
Lung, lymph nodes	Bone, liver, lymph nodes

3. This child has the *diencephalic syndrome.* This syndrome is a rare symptom complex associated with neoplasms of the brain in the region of the hypothalamus and third ventricle, and is characterized by vomiting, failure to thrive, euphoria and alertness. Excessive sweating, polyuria and nystagmoid movements of the eye may also occur. Characteristically these children, while responding to pain with the appropriate affect, do not sustain crying for any length of time.

The syndrome usually has its onset at the age of 2-5 months, and is fatal in a year. In the older child, diencephalic neoplasms are often associated with obesity, sexual precocity and somnolence. This is in contrast to the case presented here with emaciation, no sexual precocity and excitation.

Other more common causes to entertain in the happy but hungry child are feeding problems (vis., not enough), fibrocystic disease and hyperthyroidism.

4. This patient's abdominal distension, while part of the picture of "malabsorption", is also increased by the presence of a mass—a functioning *ganglioneuroma.* This tumor, while usually non-functioning, can present with symptoms of diarrhea, hypertension, hypermetabolism, nausea, vomiting, etc., due to the release of epinephrine and norepinephrine from the tumor. Diagnosis can be made by assessing urinary VMA levels or administering a sympathetic blocker; e.g., phentolamine (Regitine). Provocative tests (e.g., histamine) are seldom indicated. Surgical removal of the tumor results in remission of the hypertension and gastro-intestinal symptoms.

1
"222"
3
4
5
6
7
"282"
"292"

basic numbers for individualized pain control

Codeine, combined with acetylsalicylic acid, phenacetin and caffeine, continues to be preferred for the relief of pain. By varying the amount of codeine in this combination, adjustment to individual needs and circumstances is provided.

"222" TABLETS (white)
Codeine phosphate..... ⅛ gr.

Ⓝ"282" TABLETS (yellow)
Codeine phosphate..... ¼ gr.

Ⓝ"292" TABLETS (pink)
Codeine phosphate..... ½ gr.

→ C { Acetylsalicylic acid 3½ gr.
Phenacetin ..... 2½ gr.
Caffeine citrate... ½ gr.

Dosage: One or two tablets as required.
Ⓝ Telephone narcotic prescription permitted.

and when codeine is not required
"217" TABLETS—the synergistic formula basic to Frosst analgesic products.

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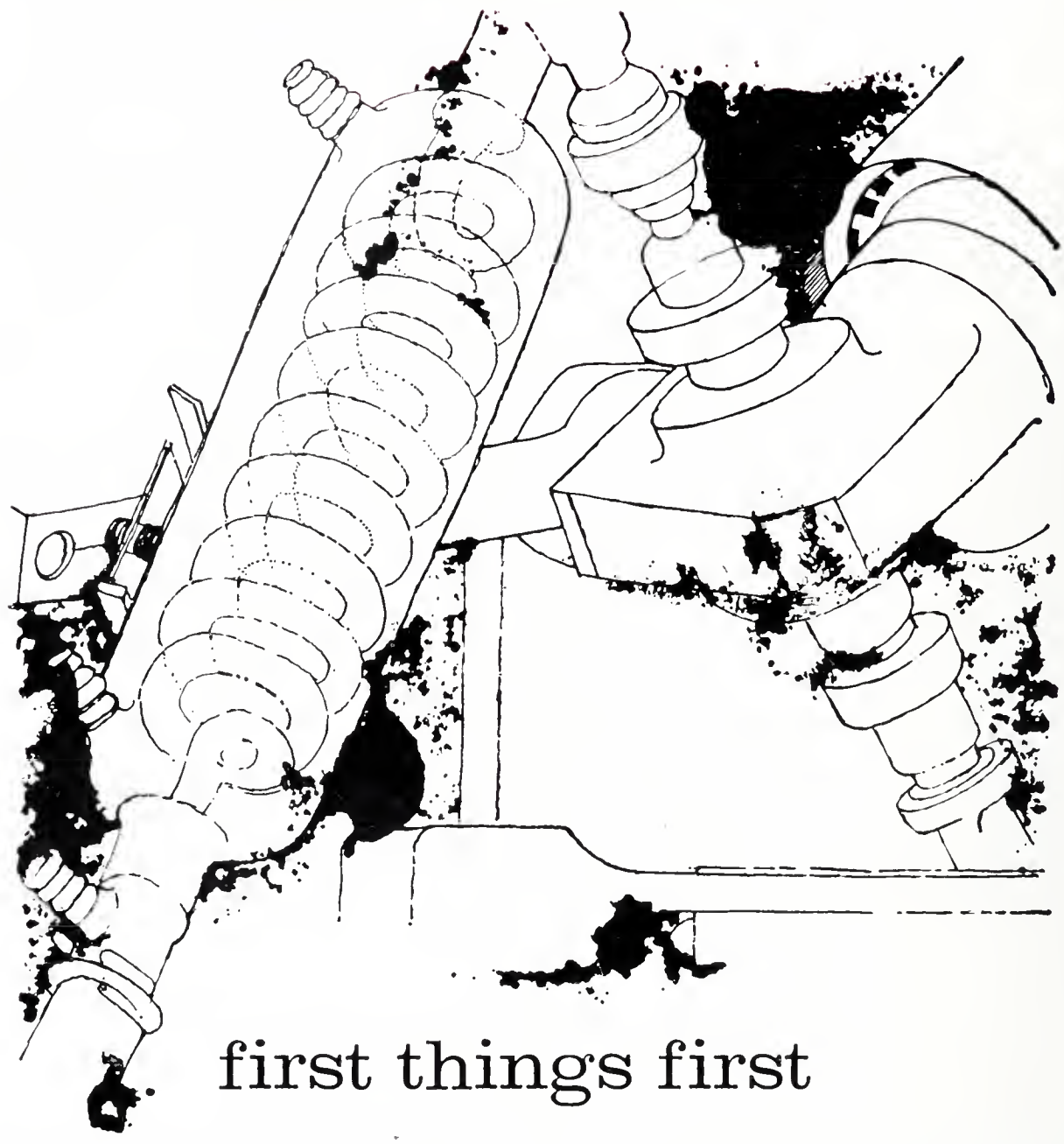

first things first

When Smith Kline & French of Canada decided it was time to move into larger quarters, there was no question whose needs would get first consideration. That's why, in 1964, our Research and Development people — physicians, biologists, chemists and pharmacologists — have preceded the rest of us in moving to Senneville, on the western tip of Montreal Island. There they will occupy newly-completed facilities at the heart of SK&F's integrated pharmaceutical centre, the remainder of which will be constructed over the next few years.

This move not only reflects the growth of our Company, but emphasizes our belief that research is the lifeblood of our business. Increased laboratory space and the most up-to-date equipment are essential to our continuing efforts to make better medicines for Canadian physicians and their patients.

(As you may know, we already manufacture a considerable number of widely prescribed ethical pharmaceuticals. You can find out about them by consulting Vademecum International, or by writing directly to us.)

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